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(57) Abstract

Disclosed are methods for synthesizing very large collections of diverse dihydropyridine, dihydropyrimidine, pyridine or pyrimidine compounds on solid supports. Also disclosed are methods for identifying and isolating dihydropyridine and dihydropyrimidine compounds with useful and diverse activities from such collections including the incorporation of identification tags in such collections to facilitate identification of compounds with desired properties.

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Methods for Synthesiszing Diverse Collections of Pyridines, Pyrimidines, 1,4-Dihydro Derivatives Thereof, and Piperidine Derivatives

BACKGROUND OF THE INVENTION

Field of the Invention

This invention is directed to methods for synthesizing very large collections of diverse 1,4-dihydropyridine, 1,4-dihydropyrimidine, pyridine pyrimidine and piperidine compounds on solid supports. This invention is further directed to methods for identifying and isolating 1,4-dihydro-pyridine, 1,4-dihydropyrimidine, pyridine, pyrimidine and piperidine compounds with useful and diverse activities from such collections. This invention is still further directed to the incorporation of identification tags in such collections to facilitate identification of compounds with desired properties.

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[2] Dower, et al., "*Method of Synthesising Diverse Collections of Oligomers*", U.S. Patent Application Serial No. 07/946,239, filed September 16, 1992

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[28] Boecker, et al., J. Med. Chem., 29:1596 (1986)

[29] Gallop, et al., U.S. Patent Application Serial No. 08/577,203 filed December 22, 1995 for METHODS FOR HARD TAGGING AN ENCODED SYNTHETIC LIBRARY

All of the above publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

State of the Art

Compounds having biological activity can be identified by screening diverse collections of compounds (i.e., libraries of compounds) produced through either molecular biological or synthetic chemical techniques. Such screening methods include methods wherein each member of the library is tagged with a unique identifier tag to facilitate identification of compounds having biological activity[1,2] or where the library comprises a plurality of compounds synthesized at specific locations on the surface of a solid substrate wherein a receptor is appropriately labeled to identify binding to the compound, e.g., fluorescent or radioactive labels. Correlation of the labelled receptor bound to the substrate with its location on the substrate identifies the binding compound.[3]

Central to these methods is the screening of a multiplicity of compounds in the library and the ability to identify the structures of the compounds which have a requisite biological activity. Preferably, in order to facilitate synthesis and identification, the compounds in the library are typically formed on solid supports wherein the compound is covalently attached to the support via a cleavable or non-cleavable linking arm. In this regard, libraries of diverse compounds are prepared and can be

screened either on the solid support or as cleaved products to identify "lead compounds" having good biological activity.

Pharmaceutical drug discovery relies heavily on studies of structure-activity relationships wherein the structure of "lead compounds" is typically altered to determine the effect of the alteration on activity. Alteration of the structure of the lead compounds permits evaluation of the effect of the structural alteration on activity. Thus libraries of compounds derived from a lead compound can be created by including derivatives of the lead compound and repeating the screening procedures.

Ideally, the compounds are synthesized *in situ* on the solid support so that the support can be tagged to identify the synthetic steps employed and/or the derivative incorporated onto the support. The use of solid supports also facilitates isolation of the compounds and intermediates thereof during synthesis. However, relatively simple synthetic methods to produce a diverse collection of such derivatives on the supports are often not available.

Particular classes of compounds which would be useful for inclusion in screening libraries are 1,4-dihydropyridine, 1,4-dihydropyrimidine, pyridine, pyrimidine and piperidine compounds. Specifically, 1,4-dihydropyridines are the largest class of organic calcium channel modulators having therapeutic utility in the treatment of cardiac arrhythmias, hypertension, angina pectoris, supraventricular tachycardia, ventricular tachyarrhythmia, congestive heart failure, asthma, cerebral insufficiency and vasospams, and in the protection against ischemic heart damage.[4,5,8] Such compounds typically contain an aryl or substituted aryl functionality at the 4 position of the 1,4-dihydropyridine, however, 4-heterocyclic and 4-alkyl substituents also have been reported as possessing calcium channel modulating activity.[6,7]

Additionally, 1,4-dihydropyridines are employed extensively as biological tools for studies of voltage-activated calcium channel structure and function[8], and 4-heterocyclic substituents of 1,4-dihydropyridine compounds have been disclosed for use as liver protecting agents.[9,10] 4-Alkyl and 4-aryl-1,4-dihydropyridines have also been disclosed as inhibiting platelet aggregation including, for example, platelet aggregation induced by PAF-acether (1-*O*-hexadecyl/octadecyl-2-*O*-acetyl-*sn*-glycero-3-phosphorylcholine)[11] and platelet aggregation induced by B16 amelanotic melanoma.[12] Fused 1,4-dihydropyridines, such as pyrido[2,3-d]pyrimidines have also been shown to possess antihypertensive activity.[13] Other disclosed and/or potential biological activities for 1,4-dihydropyridines include antioxidant, antitumor, antimutagenic, geroprotective, anti-atherosclerotic, antifungal, antiviral, antibacterial, bronchodilating, and antidiabetic activity.[27]

1,4-Dihydropyrimidine compounds have been shown to mimic the biological effect of 1,4-dihydropyridines including calcium channel blocking activity and possess vasorelaxant and antihypertensive activities.[8,14,15,17]

Pyridine compounds have been disclosed as inhibiting release of myeloperoxidase from polymorphonuclear leukocytes (PMN) which, in turn, is theorized to modulate the tissue destructive nature of adult respiratory distress syndrome.[25] Such compounds as well as pyrimidine structures have also been disclosed as possessing anticonvulsant activity in mice[24]. Additionally, pyridine compounds have been disclosed as possessing zinc chelating properties which can inhibit the binding of HIV-EP1 to NF-κB recognition sequence.[23]

Pyrimidine derivatives have also been disclosed as inhibiting human leukocyte elastase thereby providing useful therapy in disease conditions

where elastase activity is ineffectively controlled by endogenous inhibitors.[26]

The myriad of therapeutic uses of 1,4-dihydropyridine, 1,4-dihydropyrimidine, pyridine and pyrimidine structures renders the generation of libraries of these compounds particularly desirable. However, while a variety of solution phase techniques have been developed to prepare 1,4-dihydropyridines and 1,4-dihydropyrimidines[16,17], including enantioselective synthesis[18,19], the incorporation of 1,4-dihydropyridines and/or 1,4-dihydropyrimidine derivatives on solid supports to form libraries of these compounds is not previously known. At best, the art discloses the preparation of a single dihydropyridine compound to a polymer via reaction of a 1,5 diketone compound via a HN_2-$(CH_2)_n$-polymer to form a non-cleavable linkage to the polymer.[27]

The ability to synthesize a multiplicity of such derivatives on a solid support or on different solid supports would enhance the structural variation of library of these compounds and provide important structure-activity information. Moreover, subsequent oxidation of the 1,4-dihydropyridine and 1,4-dihydropyrimidine structures would yield pyridine and pyrimidine libraries. Libraries of other pyrimidine compounds prepared via alternative routes would also be desirable.

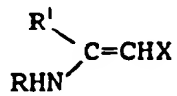
SUMMARY OF THE INVENTION

This invention is directed to synthetic methods for incorporating a 1,4-dihydropyridine, a 1,4-dihydropyrimidine, a pyridine, a pyrimidine or a piperidine group onto a solid support which methods can be employed in conjunction with known stochastic methods for preparing libraries of compounds comprising one or more such groups.

Solid supports containing such 1,4-dihydropyridine, 1,4-dihydropyrimidine, pyridine, pyrimidine or piperidine groups preferably comprise a linking arm which links the solid support to the group. The linking arm can be either cleavable or non-cleavable and when cleavable, can be used to prepare a library of soluble 1,4-dihydropyridine, 1,4-dihydropyrimidine, pyridine, pyrimidine or piperidine compounds. The library of such compounds, whether soluble or insoluble, can be screened to isolate individual compounds that possess some desired biological activity. In a preferred embodiment, each compound in the library is unique.

Accordingly, in one aspect of the methods described herein, 1,4-dihydropyridine groups, 1,4-dihydropyrimidine, pyridine, pyrimidine or piperidine groups covalently attached to a solid support are prepared by providing for a Knoevenagel condensation product of an aldehyde and a compound selected from a β-keto ester, a β-keto amide and a β-diketone and contacting this Knoevenagel condensation product with either an enamino compound under conditions effective to provide for the 1,4-dihydropyridine group or with an amidine compound under conditions effective to provide for the 1,4-dihydropyrimidine group wherein the Knoevenagel condensation product or the enamino/amidine compound is covalently attached to a solid support and further wherein the 1,4-dihydropyridine or 1,4-dihydropyrimidine group is optionally oxidized to a pyridine or a pyrimidine group respectively or the 1,4-dihydropyridine is optionally reduced to the piperidine group.

Preferred enamino compounds are represented by the formula:



where R is selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms;

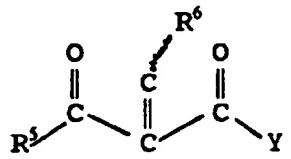
R^1 is selected from the group consisting of hydrogen, alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and 1 to 5 halo atoms, thioalkyl of from 1 to 6 carbon atoms, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, aryl of from 6 to 10 carbon atoms optionally substituted with from 1 to 2 substituents selected from the group consisting of nitro, cyano, halo, alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, and $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms; and

X is selected from the group consisting of $-C(O)R^2$, $-S(O)_2R^2$, cyano, nitro, and $-PO(NR^3R^4)_2$, $-PO(OR^{12})_2$ where R^2 is alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkoxy of from 1 to 6 carbon atoms, alkalkoxy of from 2 to 8 carbon atoms and from 1 to 3 ether oxygens, alkamino of from 2 to 6 carbon atoms, N-alkylalkamino of from 2 to 10 carbon atoms and N,N-dialkylalkamino of from 3 to 12 carbon atoms, R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, and R^{12} is selected from the group consisting of alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkalkoxy of from 2 to 8 carbon atoms and from 1 to 3 ether oxygens, alkamino of from 2 to 6 carbon atoms, N-alkylalkamino of from 2 to 10 carbon atoms and N,N-dialkylalkamino of from 3 to 12 carbon atoms,

wherein, optionally, the enamino compound is covalently attached to a compatible solid support via the R, R^1 or X substituent.

Preferably, the Knoevenagel condensation product is formed by contacting an alkyl or aromatic aldehyde with a compound selected from a β-keto ester, a β-keto amide and a β-diketone where optionally the keto

group is masked under conditions which effect condensation. Preferred Knoevenagel condensation products are represented by the formula:



wherein

R^5 is hydrogen, a linear alkyl group of from 1 to 6 carbon atoms or an aryl group of from 6 to 10 carbon atoms,

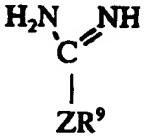
R^6 is alkyl of from 1 to 6 carbon atoms, aryl of from 6 to 10 carbon atoms optionally substituted with from 1 to 2 substituents selected from the group consisting of nitro, cyano, halo, alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkoxy of from 1 to 6 carbon atoms, carboxyl and $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, or a heterocyclic group of from 2 to 9 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, and

Y is selected from the group consisting of alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkoxy of from 1 to 6 carbon atoms, alkalkoxy of from 2 to 8 carbon atoms and from 1 to 3 ether oxygens, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms and optionally Y and R^5 are joined to form a cyclic or heterocylic structure fused to the 1,4-dihydropyridine ring which structure contains from 2 to 6 carbon atoms and optionally from 1 to 3 hetero atoms selected from oxygen, nitrogen and sulfur

still further wherein, optionally, the condensation product is covalently attached to a compatible solid support via the Y or R^6 substituent.

Preferably, the Knoevenagel condensation product is formed in the presence of the enamino compound so that upon condensation, it *in situ* reacts with the enamino compound to provide for a 1,4-dihydropyridine group.

Preferred amidine compounds include 2-aminoimidazoles, (2-amino)arylimidazoles and compounds represented by the formula:



wherein R^9 is selected from the group consisting of hydrogen, alkyl of from 1 to 6 carbon atoms optionally substituted with from 1 to 5 substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, alkoxy of from 1 to 6 carbon atoms, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, carboxyl, and $-C(O)NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, aryl of from 6 to 10 carbon atoms optionally substituted with from 1 to 3 substituents selected from halogen, hydroxy, nitro, cyano, alkyl of from 1 to 6 carbon atoms and alkoxy of from 1 to 6 carbon atoms, alkaryl of from 7 to 12 carbon atoms optionally substituted with from 1 to 3 substituents on the aryl ring which substituents are selected from halogen, hydroxy, nitro, cyano, alkyl of from 1 to 6 carbon atoms and alkoxy of from 1 to 6 carbon atoms, heterocyclic of from 2 to 5 carbon atoms and from 1 to 3 hetereoatoms selected from oxygen, nitrogen and sulfur, and an amino acid residue; and

Z is selected from the group consisting of O, NH and S.

Optionally, the amidine compound is covalently linked to a compatible solid support via the imidazole ring or the Z substituent.

The amidine compounds described above can be reacted directly with a β-diketone to provide for pyrimidine libraries without the need for oxidation. In this embodiment, either the β-diketone or the amidine compound is attached to a solid support.

The solid supports prepared in the methods described above can be used, for example, in creating libraries of compounds in the manner described in International Patent Application Publication No. WO 93/06121[1] or in creating solid supports such as those described in U.S. Patent No. 5,143,854[2], to screen the compounds for biological activity. The disclosures of International Patent Application Publication No. WO 93/06121 and U.S. Patent No. 5,143,854 are incorporated herein by reference in their entirety.

Accordingly, in one of its composition aspects, this invention is directed to a library of diverse 1,4-dihydropyridine, 1,4-dihydropyrimidine, pyridine, pyrimidine or piperidine structures comprising a plurality of solid supports having a plurality of covalently bound 1,4-dihydropyridine, 1,4-dihydropyrimidine, pyridine, pyrimidine or piperidine groups wherein the 1,4-dihydropyridine, the 1,4-dihydropyrimidine, the pyridine, the pyrimidine, or the piperidine group bound to each of the supports is substantially homogeneous and further wherein each compound bound on one support is different from the compounds bound on the other supports.

Preferably, the library described herein contains on the solid supports a surface bound tag which identifies the molecule attached thereto.

This invention is also directed to methods for preparing a synthetic 1,4-dihydropyridine, 1,4-dihydropyrimidine, pyridine, pyrimidine or piperidine compound library produced by synthesizing on each of a plurality of solid supports a single compound wherein each compound

comprises either a 1,4-dihydropyridine group, a 1,4-dihydropyrimidine group, a pyridine group, a pyrimidine or a piperidine group, which library is synthesized in a process comprising:

a) apportioning the supports comprising a covalently bound Knoevenagel condensation product or a covalently bound compound selected from the group consisting of an enamino group or an amidine group among a plurality of reaction vessels, and

b) exposing the supports in each reaction vessel under conditions wherein the condensation product or the enamino group is converted to a 1,4-dihydropyridine group or wherein the condensation product or the amidine group is converted to a 1,4-dihydropyrimidine group provided that at least one of the following conditions is satisfied:

1) at least two different Knoevenagel condensation products are used to produce the 1,4-dihydropyridine or 1,4-dihydropyrimidine groups;

2) at least two different enamino or amidine groups are used to produce the 1,4-dihydropyridine or 1,4-dihydropyrimidine groups; and

3) at least two different sets of reaction conditions are used to produce the 1,4-dihydropyridine or the 1,4-dihydropyrimidine groups

wherein the 1,4-dihydropyridine or the 1,4-dihydropyrimidine groups are optionally oxidized to pyridine and pyrimidine groups respectively or the 1,4-dihydropyridine group is optionally reduced to a piperidine group.

In this method, 1,4-dihydropyridine compounds bound to a solid support are prepared by contacting the Knoevenagel condensation product with an enamino compound wherein either the condensation product or the enamino compound is covalently attached to a solid support.

Contrarily, 1,4-dihydropyrimidine compounds bound to a solid support are prepared by contacting the Knoevenagel condensation product with an amidine compound wherein either the condensation product or the amidine compound is covalently attached to a solid support.

This invention is still further directed to a method for preparing a synthetic 1,4-dihydropyridine, 1,4-dihydropyrimidine, pyridine, pyrimidine or piperidine compound library which library is synthesized in a process comprising:

a) apportioning supports comprising a linking arm having a reactive amino or hydroxyl functionality into a plurality of reaction vessels,

b) combining into each reaction vessel a different β-keto ester, β-keto amide or β-diketone such that the β-keto ester, β-keto amide or β-diketone becomes covalently attached to the linking arm of the supports through the amino or hydroxyl functionality,

c) pooling the supports and then apportioning the supports among a plurality of reaction vessels,

d) combining into each reaction vessel a different aldehyde under conditions wherein the β-keto ester, the β-keto amide or the β-diketone forms a Knoevenagel condensation product with the aldehyde,

e) pooling the supports produced in d) above and then apportioning the supports among a plurality of reaction vessels,

f) combining into each reaction vessel a different enamino group or a different amidine group under conditions wherein the Knoevenagel condensation product and the enamino or amidine group form an adduct,

g) cyclizing the adduct to form a 1,4-dihydropyridine compound when an enamino group is employed and a 1,4-dihydropyrimidine compound when an amidine group is employed, and

h) optionally oxidizing the 1,4-dihydropyridine or 1,4-dihydropyrimidine compound to the pyrdine or pyrimidine compound respectively or optionally reducing the 1,4-dihydropyridine compound to a piperidine compound.

In one embodiment, the adduct prepared in procedure f) is separated from the support and then cyclized to either the 1,4-dihydropyridine compound or the 1,4-dihydropyrimidine compound.

In another embodiment, the 1,4-dihydropyridine group or the 1,4-dihydropyrimidine group is first cyclized on the solid support and then optionally separated from the support to provide for soluble 1,4-dihydropyridine and 1,4-dihydropyrimidine compounds.

In another of its method aspects, this invention is directed to a method for preparing a synthetic 1,4-dihydropyridine, pyridine or piperidine compound library which library is synthesized in a process comprising:

a) apportioning supports comprising a linking arm having a reactive amino or hydroxyl functionality into a plurality of reaction vessels,

b) combining into each reaction vessel a different enamino group or an enamino precursor group such that the enamino group or the enamino precursor group becomes covalently attached to the linking arm through the amino or hydroxyl functionality wherein, in the case of the enamino precursor groups, the attachment converts the enamino precursor group to an enamino group,

c) pooling the supports and then apportioning the supports among a plurality of reaction vessels,

d) combining into each reaction vessel a different Knoevenagel condensation product under conditions wherein the Knoevenagel condensation product and the enamino group form an adduct,

e) cyclizing the adduct to form a 1,4-dihydropyridine compound, and

f) optionally oxidizing or reducing the 1,4-dihydropyridine compound produced in e) above to a pyridine or piperidine compound.

In still another of its method aspects, this invention is directed to a method for preparing a synthetic 1,4-dihydropyrimidine or pyrimidine compound library which library is synthesized in a process comprising:

a) apportioning supports comprising a linking arm having a reactive amino or hydroxyl functionality into a plurality of reaction vessels,

b) combining into each reaction vessel a different amidine group or an amidine precursor group such that the amidine group or the amidine precursor group becomes covalently attached to the linking arm through the amino or hydroxyl functionality wherein, in the case of the amidine precursor groups, the attachment converts the amidine precursor group to an amidine group,

c) pooling the supports and then apportioning the supports among a plurality of reaction vessels,

d) combining into each reaction vessel a different Knoevenagel condensation product under conditions wherein the Knoevenagel condensation product and the amidine group form an adduct,

e) cyclizing the adduct to form a 1,4-dihydropyrimidine compound, and

f) optionally oxidizing the 1,4-dihydropyrimidine compound produced in e) above to the pyrimidine compound.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates one means for the covalent attachment of keto esters on solid supports. FIG. 1 also illustrates conversion of the resin bound keto ester to 3-methyl-3-pyrazoline-5-one as a basis to determine the loading efficiency of the keto ester to the resin.

FIG. 2 illustrates the solid phase synthesis of 1,4-dihydropyridine compounds attached to a Wang solid support via the 3-carboxyl group of the 1,4-dihydropyridine and subsequent oxidation of the 1,4-dihydropyridine compound to the pyridine compound.

FIG. 3 illustrates the preparation of 1,4-dihydropyridine compounds via a solid support prepared using an N-immobilized enamino ester.

FIG. 4 illustrates the solid phase synthesis of 1,4-dihydropyrimidine compounds on a solid support via the 3-carboxyl group of the 1,4-dihydropyrimidine and subsequent separation of these compounds from the solid support to provide for a solution phase library of these compounds.

FIG. 5 illustrates the preparation of a library of 1,4-dihydropyridine compounds via the use of solid phase tethered enamino compounds.

FIG. 6 illustrates the synthesis of a library of pyrimidine compounds from amidine compounds tethered to a solid support and β-diketones.

FIG. 7 illustrates the use of an amino acid bound to a solid support to effect solid phase synthesis of dihydropyridines.

FIG. 8, illustrates that the use of 2-aminouracil in place of an enamino compound leads to the solid phase synthesis of pyrido[2,3-d]pyrimidine compounds.

FIG. 9 is a synthetic scheme for preparing immobilized keto esters.

FIG. 10 illustrates the guanylation reactions on solid phase amino acids.

FIG. 11 illustrates the solid phase synthesis of nicotinic acids and pyrido[2,3-d]pyrimidines.

DETAILED DESCRIPTION OF THE INVENTION

This invention is directed to synthetic methods for preparing 1,4-dihydropyridine, 1,4-dihydropyrimidine, pyridine, pyrimidine and piperidine compounds on solid supports and the use of these methods to incorporate such compounds into large synthetic compound libraries.

Prior to discussing this invention in further detail, the following terms will first be defined:

Definitions

The term "calcium antagonist" or "calcium channel blocker" refers to a compound that alters the cellular function of calcium by inhibiting calcium entry into a cell and/or calcium release from a cell and/or interfering with one or more intracellular actions of calcium.

The term "calcium agonist" refers to a compound that increases the amount of calcium entering or releasing from a cell.

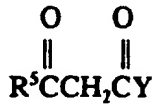
The term "calcium modulators" refers to those compounds which are either calcium agonists or antagonists.

The term "substrate" or "solid support" refers to a material having a rigid or semi-rigid surface which contains or can be derivatized to contain reactive functionality which covalently links a compound to the surface thereof. Such materials are well known in the art and include, by way of example, silicon dioxide supports containing reactive Si-OH groups, polyacrylamide supports, polystyrene supports, polyethyleneglycol supports, and the like. Such supports will preferably take the form of small beads, pellets, disks, or other conventional forms, although other forms may be used. In some embodiments, at least one surface of the substrate will be substantially flat.

The term "β-keto ester, β-keto amide and β-diketone" refers to compounds having a ketone or aldehyde carbonyl (>C=O) functionality in a position *beta* to an ester, amide or ketone functionality wherein these compounds have a methylene group interposed between the carbonyl functionality and the ester, amide or ketone functionality which compounds

are reactive with an aldehyde to form a Knoevenagel condensation product.

The β-keto ester, β-keto amide or β-diketone compound employed is not critical but preferably has no more than about 20 carbon atoms. Particularly preferred β-keto ester, β-keto amide or β-diketone compounds are represented by the formula:



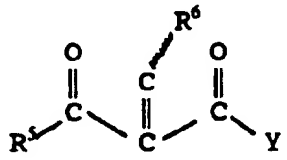
R^5 is hydrogen, a linear alkyl group of from 1 to 6 carbon atoms or an aryl group of from 6 to 10 carbon atoms, and Y is selected from the group consisting of alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkoxy of from 1 to 6 carbon atoms, alkalkoxy of from 2 to 8 carbon atoms and from 1 to 3 ether oxygens, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms and optionally Y and R^5 are joined to form a cyclic or heterocylic structure fused to the 1,4-dihydropyridine ring which structure contains from 2 to 6 carbon atoms and optionally from 1 to 3 hetereo atoms selected from oxygen, nitrogen and sulfur

still further wherein, optionally, the condensation product is covalently attached to a compatible solid support via the Y substituent.

The term "Knoevenagel condensation product" refers to the condensation product formed between an aldehyde and a β-keto ester, a β-keto amide, or a β-diketone. Condensation of the aldehyde with such β-keto compounds results in the formation of unsaturation at the carbon atom intermediate between the β-keto functionality and the ester, amide or ketone functionalities. Knoevenagel condensation products are known *per se* in the art and the particular product employed is not critical.

The aldehyde employed to prepare the Knoevenagel condensation product is not critical and can be an aromatic, heterocyclic or alkyl aldehyde preferably having no more than 20 carbon atoms.

Preferred Knoevenagel condensation products are represented by the formula:



wherein

R^5 is hydrogen, a linear alkyl group of from 1 to 6 carbon atoms or an aryl group of from 6 to 10 carbon atoms,

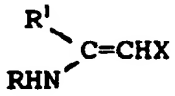
R^6 is an alkyl group of from 1 to 6 carbon atoms, an aryl group of from 6 to 10 carbon atoms optionally substituted with from 1 to 2 substituents selected from the group consisting of nitro, cyano, halo, alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkoxy of from 1 to 6 carbon atoms, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, and carboxyl, or a heterocyclic group of from 2 to 9 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, and

Y is selected from the group consisting of alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkoxy of from 1 to 6 carbon atoms, alkalkoxy of from 2 to 8 carbon atoms and from 1 to 3 ether oxygens, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms and optionally Y and R^5 are joined to form a cyclic or heterocylic structure fused to the 1,4-dihydropyridine ring which structure contains from 2 to 6 carbon atoms and optionally from 1 to 3 hetero atoms selected from oxygen, nitrogen and sulfur

still further wherein, optionally, the condensation product is covalently attached to a compatible solid support via the Y or R^6 substituent.

The term "enamino compound (group or functionality)" refers to those compounds, groups and functionalities having an enamino moiety (i.e., C=C-NH) which is reactive with Knoevenagel condensation products to form 1,4-dihydropyridine compounds. Compounds comprising an enamino moiety are known *per se* in the art and the particular compound employed is not critical.

Preferred enamino compounds are represented by the formula:



where R is selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms;

R^1 is selected from the group consisting of hydrogen, alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and 1 to 5 halo atoms, thioalkyl of from 1 to 6 carbon atoms, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, aryl of from 6 to 10 carbon atoms optionally substituted with from 1 to 2 substituents selected from the group consisting of nitro, cyano, halo, alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, and $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms; and

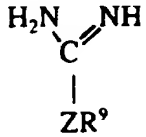
X is selected from the group consisting of $-C(O)R^2$, $-S(O)_2R^2$, cyano, nitro, and $-PO(NR^3R^4)_2$, $-PO(OR^{12})_2$ where R^2 is alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5

halo atoms, alkoxy of from 1 to 6 carbon atoms, alkalkoxy of from 2 to 8 carbon atoms and from 1 to 3 ether oxygens, alkamino of from 2 to 6 carbon atoms, N-alkylalkamino of from 2 to 10 carbon atoms and N,N-dialkylalkamino of from 3 to 12 carbon atoms, R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, and R^{12} is selected from the group consisting of alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkalkoxy of from 2 to 8 carbon atoms and from 1 to 3 ether oxygens, alkamino of from 2 to 6 carbon atoms, N-alkylalkamino of from 2 to 10 carbon atoms and N,N-dialkylalkamino of from 3 to 12 carbon atoms,

wherein, optionally, the enamino compound is covalently attached to a compatible solid support via the R, R^1 or X substituent.

The term "amidine compound (group or functionality)" refers to those compounds, groups and functionalities having an amidine moiety which is reactive with Knoevenagel condensation products to form 1,4-dihydropyrimidine compounds. Compounds comprising an amidine moiety are known *per se* in the art and the particular compound employed is not critical.

Preferred amidine compounds include 2-aminoimidazoles, (2-amino)arylimidazoles of 6 to 10 carbon atoms in the aryl group, 2-aminoarylimidazoles of 6 to 10 carbon atoms in the aryl group (e.g., benzimidazoles) and compounds represented by the formula:



wherein R^9 is selected from the group consisting of hydrogen, alkyl of from 1 to 6 carbon atoms optionally substituted with from 1 to 5 substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, alkoxy of from 1 to 6 carbon atoms, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, carboxyl, and $-C(O)NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, aryl of from 6 to 10 carbon atoms optionally substituted with from 1 to 3 substituents selected from halogen, hydroxy, nitro, cyano, alkyl of from 1 to 6 carbon atoms and alkoxy of from 1 to 6 carbon atoms, alkaryl of from 7 to 12 carbon atoms optionally substituted with from 1 to 3 substituents on the aryl ring which substituents are selected from halogen, hydroxy, nitro, cyano, alkyl of from 1 to 6 carbon atoms and alkoxy of from 1 to 6 carbon atoms, heterocyclic of from 2 to 5 carbon atoms and from 1 to 3 hetereoatoms selected from oxygen, nitrogen and sulfur, and an amino acid residue (of from 1 to 30 residues in length); and

Z is selected from the group consisting of O, NH and S.

Optionally, the amidine compound is covalently linked to a compatible solid support via the imidazole ring or the Z substituent.

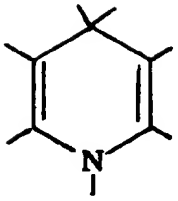
Linking arms are well known in the art and include, by way of example only, conventional linking arms such as those comprising ester, amide, carbamate, ether, thioether, urea, amine and the like linking groups. The linking group is formed by coupling complementary reactive groups found on the linking arm and the compound to be attached. For example, an amide linking group can be formed by reacting an amine functionality on the linking arm with an carboxylic acid or ester functionality on the compound to be linked. Similarly, an ester linking arm can be formed by reacting a hydroxyl functionality on the linking arm with an carboxylic acid or ester functionality on the compound to be linked.

The linking arm can be cleavable or non-cleavable. "Cleavable linking arms" refer to linking arms wherein at least one of the covalent bonds of the linking arm which attaches the compound comprising the 1,4-dihydropyridine, the 1,4-dihydropyrimidine group, the pyridine group or the pyrimidine group to the solid support can be readily broken by specific chemical reactions thereby providing for such compounds free of the solid support ("soluble compounds"). The chemical reactions employed to break the covalent bond of the linking arm are selected so as to be specific for bond breakage thereby preventing unintended reactions occurring elsewhere on the compound. The cleavable linking arm is selected relative to the synthesis of the compounds to be formed on the solid support so as to prevent premature cleavage of this compound from the solid support as well as not to interfere with any of the procedures employed during compound synthesis on the support.

Suitable cleavable linking arms are well known in the art and include photolabile linking arms such as those disclosed in U.S. Patent No. 5,143,854 and the commercially available Rink resin with 4-[(2',4'-dimethoxyphenyl)-aminomethyl]phenoxy linking arms which is a super acid-labile linking arm.

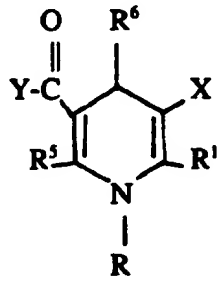
"Non-cleavable linking arms" refer to linking arms wherein the covalent bond(s) linking the 1,4-dihydropyridine, the 1,4-dihydropyrimidine, the pyridine and the pyrimidine group to the solid support can only be cleaved under conditions which chemically alters unintended parts of the structure of the compound attached thereto.

The term "1,4-dihydropyridine" refers to compounds having the base or core structure of



Substituents to the 1,4-dihydropyridine group can occur at any of the 1, 2, 3, 4, 5 and 6 positions thereof including the nitrogen atom in the manner depicted above. Such substituents are governed solely by the reagents employed thereby providing flexibility in preparing a large library of 1,4-dihydropyridine compounds.

In a preferred embodiment, the 1,4-dihydropyridine compounds (or groups) have the formula



where R is selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms;

R^1 is selected from the group consisting of hydrogen, alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and 1 to 5 halo atoms, thioalkyl of from 1 to 6 carbon atoms, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, aryl of from 6 to 10 carbon atoms optionally substituted with from 1 to 2 substituents selected from the group consisting of nitro, cyano, halo, alkyl of from 1 to 6 carbon atoms, haloalkyl of from

1 to 2 carbon atoms and from 1 to 5 halo atoms, and -NR^3R^4 where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms;

R^5 is hydrogen, a linear alkyl group of from 1 to 6 carbon atoms or an aryl group of from 6 to 10 carbon atoms,

R^6 is alkyl of from 1 to 6 carbon atoms, aryl of from 6 to 10 carbon atoms optionally substituted with from 1 to 2 substituents selected from the group consisting of nitro, cyano, halo, alkyl of from 1 to 6 carbon atom, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkoxy of from 1 to 6 carbon atoms, -NR^3R^4 where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms and carboxyl, or a heterocyclic group of from 2 to 9 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen,

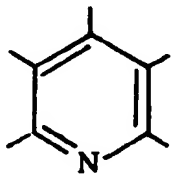
X is selected from the group consisting of -$C(O)R^2$, -$S(O)_2R^2$, cyano, nitro, -$PO(NR^3R^4)_2$ and -$PO(OR^{12})_2$ where R^2 is alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkoxy of from 1 to 6 carbon atoms, alkalkoxy of from 2 to 8 carbon atoms and from 1 to 3 ether oxygens, alkamino of from 2 to 6 carbon atoms, N-alkylalkamino of from 2 to 10 carbon atoms and N,N-dialkylalkamino of from 3 to 12 carbon atoms, R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, R^{12} is selected from the group consisting of alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkalkoxy of from 2 to 8 carbon atoms and from 1 to 3 ether oxygens, alkamino of from 2 to 6 carbon atoms, N-alkylalkamino of from 2 to 10 carbon atoms and N,N-dialkylalkamino of from 3 to 12 carbon atoms, and optionally X and R^1 are joined to form a cyclic or heterocyclic structure fused to the 1,4-dihydropyridine ring which structure contains from 3 to 6 carbon atoms and 1 to 3 hetero atoms, and

Y is selected from the group consisting of alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkoxy of from 1 to 6 carbon atoms, alkalkoxy of from 2 to 8 carbon atoms and from 1 to 3 ether oxygens, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms and optionally Y and R^5 are joined to form a cyclic or heterocylic structure fused to the 1,4-dihydropyridine ring which structure contains from 3 to 6 carbon atoms and optionally from 1 to 3 hetereo atoms selected from the group consisting of oxygen, nitrogen and sulfur,

and salts thereof

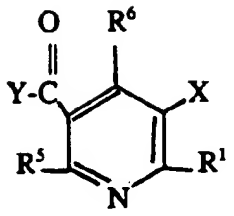
wherein said 1,4-dihydropyridine is optionally attached to a solid support through the R, R^6, Y or X substituent.

The term "pyridine" refers to compounds having the base or core structure of



Substituents to the pyridine group can occur at any of the 2, 3, 4, 5 and 6 positions thereof in the manner depicted above. Such substituents are governed solely by the reagents employed thereby providing flexibility in preparing a large library of pyridine compounds.

In a preferred embodiment, the pyridine compounds (or groups) have the formula



R^1 is selected from the group consisting of hydrogen, alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and 1 to 5 halo atoms, thioalkyl of from 1 to 6 carbon atoms, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, aryl of from 6 to 10 carbon atoms optionally substituted with from 1 to 2 substituents selected from the group consisting of nitro, cyano, halo, alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms and $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms,

R^5 is hydrogen, a linear alkyl group of from 1 to 6 carbon atoms or an aryl group of from 6 to 10 carbon atoms,

R^6 is alkyl of from 1 to 6 carbon atoms, aryl of from 6 to 10 carbon atoms optionally substituted with from 1 to 2 substituents selected from the group consisting of nitro, cyano, halo, alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkoxy of from 1 to 6 carbon atoms, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms and carboxyl, or a heterocyclic group of from 2 to 9 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen,

X is selected from the group consisting of $-C(O)R^2$, $-S(O)_2R^2$, cyano, nitro, $-PO(NR^3R^4)$ and $-PO(OR^{12})_2$ where R^2 is alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkoxy of from 1 to 6 carbon atoms, alkalkoxy of from 2 to 8

carbon atoms and from 1 to 3 ether oxygens, alkamino of from 2 to 6 carbon atoms, N-alkylalkamino of from 2 to 10 carbon atoms and N,N-dialkylalkamino of from 3 to 12 carbon atoms, R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, R^{12} is alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkalkoxy of from 2 to 8 carbon atoms and from 1 to 3 ether oxygens, alkamino of from 2 to 6 carbon atoms, N-alkylalkamino of from 2 to 10 carbon atoms and N,N-dialkylalkamino of from 3 to 12 carbon atoms, and optionally X and R^1 are joined to form a cyclic or heterocyclic structure fused to the pyridine ring which structure contains from 3 to 6 carbon atoms and optionally 1 to 3 hetero atoms selected from the group consisting of oxygen, sulfur and nitrogen, and

Y is selected from the group consisting of alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkoxy of from 1 to 6 carbon atoms, alkalkoxy of from 2 to 8 carbon atoms and from 1 to 3 ether oxygens, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms and optionally Y and R^5 are joined to form a cyclic or heterocylic structure fused to the 1,4-dihydropyridine ring which structure contains from 3 to 6 carbon atoms and optionally from 1 to 3 hetereo atoms selected from oxygen, nitrogen and sulfur,

and salts thereof

wherein said pyridine is optionally attached to a solid support through the R^6, Y or X substituent.

The term "a heterocylic structure fused to the 1,4-dihydropyridine ring" refers to structures as set forth above wherein Y and R^5 or X and R^1 are joined to form a heterocyclic ring structure which, with the carbon atoms of the 1,4-dihydropyridine structure, contains from 3 to 6 carbon

atoms and 1 to 3 hetero atoms. Preferred fused structures include those where Y and R^5 are fused to form a heterocyclic ring (e.g, Y-R^5 = -$NR^7C(O)NR^8$- where R^7 and R^8 are hydrogen or alkyl of from 1 to 6 carbon atoms, or a lactone (i.e., Y-R^5 = -Oalkylene-), and where X and R^1 are fused to form a lactone (i.e., X-R^1 = -Oalkylene-).

The term "lower alkyl" refers to straight and branched chain alkyl groups having from 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, tert-butyl, sec-butyl, n-pentyl, n-hexyl, 2-methylpentyl, and the like.

The term "lower alkoxy" refers to straight and branched chain alkoxy groups having from 1 to 6 carbon atoms, such as methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, 2-methylpentoxy, and the like.

The term "alkalkoxy" refers to substituents of the general formula -$(R^{10}O)_nR^{11}$ where R^{10} is an alkylene group of from 1 to 6 carbon atoms, R^{11} is an alkyl group of from 1 to 6 carbon atoms and n is an integer of from 1 to 3. Preferred alkalkoxy groups have from 2 to 8 carbon atoms and from 1 to 3 ether oxygens.

The term "alkamino" refers to substituents of the general formula -$R^{10}NH_2$ where R^{10} is an alkylene group of from 1 to 6 carbon atoms.

The term "N-alkylalkamino" refers to substituents of the general formula -$R^{10}NHR^{11}$ where R^{10} is an alkylene group of from 1 to 6 carbon atoms and R^{11} is an alkyl group of from 1 to 6 carbon atoms.

The term "N,N-dialkylalkamino" refers to substituents of the general formula -$R^{10}N(R^{11})_2$ where R^{10} is an alkylene group of from 1 to 6

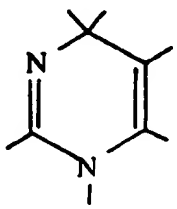
carbon atoms and each R^{11} is independently an alkyl group of from 1 to 6 carbon atoms.

The term "heterocyclic group" refers to well known cyclic groups containing from 2 to 6 carbon atoms and 1 to 3 hetereoatoms selected from nitrogen, oxygen and sulfur. Such groups include, by way of example, furazanyl, furyl, imidazolidinyl, imidazolyl, imidazolinyl, isothiazolyl, isoxazolyl, morpholinyl (e.g. morpholino), oxazolyl, piperazinyl (e.g. 1-piperazinyl), piperidyl (e.g. 1-piperidyl, piperidino), pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolidinyl (e.g. 1-pyrrolidinyl), pyrrolinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl, thiomorpholinyl (e.g. thiomorpholino), and triazolyl. These heterocyclic groups can be substituted or unsubstituted. Where a group is substituted, the substituent can be lower alkyl, lower alkoxy, halogen, substituted or unsubstituted aryl of from 6 to 10 carbon atoms and such substitution is typically from 1 to 2 independent substituents.

The term "aryl" refers to aromatic substituents comprising carbon and hydrogen such as phenyl, naphthyl and the like.

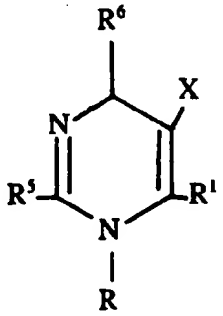
The term "alkaryl" refers to alkyl substituents having from 1 to 3 aryl substituents including, by way of example, benzyl, $-(CH_2)_2\phi$, and the like.

The term "1,4-dihydropyrimidine" refers to compounds having the base or core structure of



Substituents to the 1,4-dihydropyrimidine group can occur at any of the 1, 2, 4, 5 and 6 positions thereof in the manner depicted above. Such substituents are governed solely by the reagents employed thereby providing flexibility in preparing a large library of 1,4-dihydropyrimidine compounds.

In a preferred embodiment, the 1,4-dihydropyrimidine compounds (or groups) have the formula



R is selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms,

R^1 is selected from the group consisting of hydrogen, alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and 1 to 5 halo atoms, thioalkyl of from 1 to 6 carbon atoms, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, aryl of from 6 to 10 carbon atoms optionally substituted with from 1 to 2 substituents selected from the group consisting of nitro, cyano, halo, alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, and $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms,

R^5 is hydrogen, a linear alkyl group of from 1 to 6 carbon atoms, an aryl group of from 6 to 10 carbon atoms or $-ZR^9$ where Z and R^9 are as defined above,

R^6 is alkyl of from 1 to 6 carbon atoms, aryl of from 6 to 10 carbon atoms optionally substituted with from 1 to 2 substituents selected from the

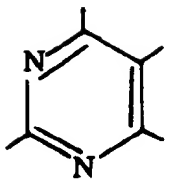
group consisting of nitro, cyano, halo, alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkoxy of from 1 to 6 carbon atoms, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms and carboxyl, or a heterocyclic group of from 2 to 9 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, and

X is selected from the group consisting of $-C(O)R^2$, $-S(O)_2R^2$, cyano, nitro, $-PO(NR^3R^4)_2$ and $-PO(OR^{12})_2$ where R^2 is alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkoxy of from 1 to 6 carbon atoms, alkalkoxy of from 2 to 8 carbon atoms and from 1 to 3 ether oxygens, alkamino of from 2 to 6 carbon atoms, N-alkylalkamino of from 2 to 10 carbon atoms and N,N-dialkylalkamino of from 3 to 12 carbon atoms, R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, R^{12} is alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkalkoxy of from 2 to 8 carbon atoms and from 1 to 3 ether oxygens, alkamino of from 2 to 6 carbon atoms, N-alkylalkamino of from 2 to 10 carbon atoms and N,N-dialkylalkamino of from 3 to 12 carbon atoms, and optionally X and R^1 are joined to form a cyclic or heterocyclic structure fused to the 1,4-dihydropyrimidine ring which structure contains from 3 to 6 carbon atoms and optionally from 1 to 3 hetero atoms selected from the group consisting of oxygen, sulfur and ntirogen,

and salts thereof

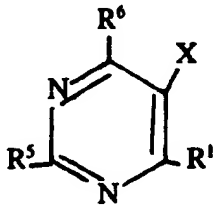
wherein said 1,4-dihydropyrimidine is optionally attached to a solid support through the R, R^6 or X substituent.

The term "pyrimidine" refers to compounds having the base or core structure of



Substituents to the pyrimidine group can occur at any of the 2, 4, 5 and 6 positions thereof in the manner depicted above. Such substituents are governed solely by the reagents employed thereby providing flexibility in preparing a large library of pyrimidine compounds.

In a preferred embodiment, the pyrimidine compounds (or groups) have the formula



R^1 is selected from the group consisting of hydrogen, alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and 1 to 5 halo atoms, thioalkyl of from 1 to 6 carbon atoms, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, aryl of from 6 to 10 carbon atoms optionally substituted with from 1 to 2 substituents selected from the group consisting of nitro, cyano, halo, alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, and $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms,

R^5 is hydrogen, a linear alkyl group of from 1 to 6 carbon atoms, an aryl group of from 6 to 10 carbon atoms, or $-ZR^9$ where Z and R^9 are as defined above,

R^6 is alkyl of from 1 to 6 carbon atoms, aryl of from 6 to 10 carbon atoms optionally substituted with from 1 to 2 substituents selected from the group consisting of nitro, cyano, halo, alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkoxy of from 1 to 6 carbon atoms, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms and carboxyl, or a heterocyclic group of from 2 to 9 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, and

X is selected from the group consisting of $-C(O)R^2$, $-S(O)_2R^2$, cyano, nitro and $-PO(OR^2)_2$ where R^2 is alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkoxy of from 1 to 6 carbon atoms, alkalkoxy of from 2 to 8 carbon atoms and from 1 to 3 ether oxygens, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, alkamino of from 2 to 6 carbon atoms, N-alkylalkamino of from 2 to 10 carbon atoms and N,N-dialkylalkamino of from 3 to 12 carbon atoms and optionally X and R^1 are joined to form a cyclic or heterocyclic structure fused to the pyrimidine ring which structure contains from 3 to 6 carbon atoms and optionally from 1 to 3 hetero atoms selected from the group consisting of oxygen, sulfur and nitrogen,

and salts thereof

wherein said pyrimidine is optionally attached to a solid support through the R^6 or X substituent.

The term "substantially homogeneous" refers to collections of molecules wherein at least 50%, preferably at least about 70%, more preferably at least about 90% and more preferably at least about 95% of the molecules are a single compound or stereoisomer thereof.

The term "stereoisomer" refers to a chemical compound having the same molecular weight, chemical composition, and constitution as another, but with the atoms grouped differently. That is, certain identical chemical moieties are at different orientations in space and, therefore, when pure, have the ability to rotate the plane of polarized light. However, some pure stereoisomers may have an optical rotation that is so slight that it is undetectable with present instrumentation. The compounds described herein may have one or more asymmetrical carbon atoms and therefore include various stereoisomers. All stereoisomers are included within the scope of the invention.

The term "removable protecting group" or "protecting group" refers to any group which when bound to a functionality such as hydroxyl, amino, or carboxyl groups prevents reactions from occurring at these functional groups and which protecting group can be removed by conventional chemical or enzymatic steps to reestablish the functional group. The particular removable protecting group employed is not critical.

The term "halogen" refers to fluorine, chlorine, bromine and iodine and preferably fluorine and chlorine.

The term "salts" refers to alkali metal, alkaline earth metal, and ammonium salts commonly employed including, by way of example, sodium, potassium, lithium, calcium, magnesium, barium, ammonium, and protamine zinc salts, which are prepared by methods well known in the art. The term also includes non-toxic acid addition salts, which are generally prepared by reacting the compounds of this invention with a suitable organic or inorganic acid. Representative salts include the hydrochloride, hydrobromide, sulfate, bisulfate, acetate, oxalate, valerate, oleate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, and napsylate salts, and the like. The particular salt

employed is not critical. Preferably, the salt is non-toxic and pharmaceutically acceptable.

Methods for Preparing 1,4-Dihydropyridine and Pyridine Compounds

The synthesis of a 1,4-dihydropyridine group on the solid support is effected by reaction of a Knoevenagel condensation product and an enamino compound. In turn, the Knoevenagel condensation product is generated by condensation of an aldehyde with a β-keto ester, a β-keto amide or a β-diketone by methods well known in the art for solution chemistry. Surprisingly, it has been found that these known methods can be conducted on solid supports wherein at least one of the Knoevenagel condensation product or the enamino compound is covalently bound to the solid support thereby providing methods for generating libraries of compounds containing 1,4-dihydropyridine groups on solid supports.

The generation of a Knoevenagel condensation product from an aldehyde and a β-keto ester, a β-keto amide or a β-diketone via solution chemistry is well documented in the art[6] and the particular route employed is not critical. However, one particularly preferred method is the treatment of a β-keto ester, a β-keto amide or a β-diketone with an aldehyde in the presence of base to provide for the condensation product. The resulting condensation product is then reacted with an enamino compound to provide for the desired 1,4-dihydropyridine compound.

An example of the entire reaction process employing a β-keto ester covalently attached to a solid support is depicted in FIGs. 1 and 2 which figures illustrate formation of a solid phase β-keto ester 3 (derived from resin 1 and a soluble β-keto ester 2); subsequent reaction of the solid phase β-keto ester 3 with aldehyde 4 forms Knoevenagel condensation product 5 which, in turn, is reacted with enamino compound 6 in the presence of a

dehydrating agent (e.g., molecular sieves) to provide for 1,4-dihydropyridine compound 7 bound to a solid support.

One such procedure for attaching the β-keto ester to the solid support is specifically illustrated in FIG. 1 with further examples set forth in Table 1 below. In this figure and table, resin 1, having a hydroxyl functionality (amine functionalities can also be used but are not illustrated), is reacted with an excess of β-keto ester, a β-keto carboxylate lithium salt in the presence of HATU and dimethylaminopyridine [DMAP], or a masked β-keto ester (i.e., diketene acetonate) in the presence of DMAP. When X is an amine functionality, it may be necessary to mask the keto group of the β-keto ester to form the amide functionality or to use a t-butyl ester. Removable masking groups are well known in the art and include, by way of example, ketal groups.

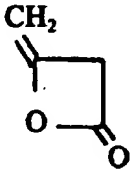
The reaction is typically conducted in a suitable inert diluent under conditions suitable to effect covalent attachment of the β-keto functionality to the solid support.

The loading of keto ester on the resins can be evaluated via cleavage/heterocyclization of the keto ester by ethanolic hydrazine with subsequent photometry of the resulting 3-methyl-3-pyrazoline-5-one 9 [ϵ=64, λ=268 nm (in 5% ethanolic hydrazine)] as illustrated in FIG. 1. The latter product is identified by, for example, nuclear magnetic resonance spectroscopy and thin layer chromatography and compared against authentic compound.

The resins employed are selected to be compatible with the keto esters and include, by way of example, commercially available TentaGel S PHB resin (contains hydroxyl functionality), Wang resin (contains hydroxyl functionality), Kaiser resin (contains hydroxyl functionality) and PAL resin

(contains amine functionality). Some typical results of keto ester loading are set forth in Table I below:

TABLE I

Keto Ester or other starting reagent	Conditions	Product Characterization via 3-methyl-3-pyrazolin-5-one	Estimated Loading mmol/g or % of theory
 (diketene)	DCM, -50°C to RT DMAP 12 hours	TLC, NMR, MS	55%
t-butyl acetoacetate	toluene 110-120°C 2.5 hours removal of t-butanol	TLC, NMR, MS, UV	0.2 mmol/g 87%
lithium acetoacetate	HATU/0.1 eq DMAP DMF-DCM (2.4:1)	TLC, UV	0.1 mmol/g 43%
lithium acetoacetate	HATU/1 eq DMAP in DMF-DCM (2.4:1)	TLC, UV	0.13 mmol/g 56%
lithium acetoacetate	PyBrop/1 eq. DMAP DMF-DCM (2.4:1)	TLC, UV	0.09 mmol/g 39%

This table establishes procedures available to prepared covalently attached keto esters to solid supports. In particular, acetoacetylation using t-butyl acetoacetate achieves about 87% loading efficiency but the

procedure employing diketene in the presence of catalytic DMAP is technically more convenient (e.g., about -50°C to RT overnight versus slow removal of t-butanol by distillation).

The procedure for converting the solid phase β-keto ester to a solid phase 1,4-dihydropyridine is specifically illustrated in FIG. 2. In this figure, β-keto ester 3 (acetoacetate covalently bound to Wang resin for illustrative purposes) is contacted with at least a stoichiometric amount and preferably from about 5 to about 50 equivalents of aldehyde 4 (C^{13}-labeled benzaldehyde for illustrative purposes) in the presence of a suitable base to form the Knoevenagel condensation product 5. The particular base employed is not critical and is selected relative to its ability to effect condensation. Preferred bases, include by way of example only, pyridine, piperidine, etc. and the base is typically employed in an amount of from about 0.1 to about 0.9 equivalents relative to the solid phase reagent.

The reaction is typically conducted in a suitable inert diluent such as acetonitrile, benzene, toluene, xylene, isopropanol, etc. under conditions sufficient to effect condensation. In a preferred embodiment, the reaction is conducted at a temperature of from about 20°C to about 100°C for a period of from about 4 to about 48 hours and preferably for from about 12 to about 24 hours. The resulting condensation product can then be recovered by conventional means such as centrifugation, filtration, etc. or alternatively is contacted with the enamino compound without recovery and/or purification.

Reaction of the Knoevenagel condensation product 5 with enamino compound 6 is typically conducted by contacting at least a stoichiometric amount of enamino compound 6 in an inert diluent optionally in the presence of a dehydrating agent (e.g., molecular sieves) to form the

1,4-dihydropyridine product 7. This reaction is conducted under conditions sufficient to effect formation of dihydropyridine product 7 and is preferably conducted at a temperature of from about 20°C to about 100°C for a period of from about 4 to about 48 hours and preferably for from about 12 to about 24 hours. Preferred solvents include, by way of example, ethanol, methanol, pyridine, dimethylformamide, N,N-dimethylacetamide (DMA).

In one embodiment, Knoevenagel condensation product formation is preferably conducted in the presence of an enamino compound which, upon *in situ* formation of the condensation product, reacts with the enamino compound to form the 1,4-dihydropyridine compound. In another embodiment, the Knoevenagel condensation product is recovered from the first reaction medium and then added to a reaction solution comprising the enamino compound.

The resulting 1,4-dihydropyridine compound 7 can be recovered by conventional methods, i.e., filtration, centrifugation, etc. Confirmation that the resin (i.e., solid support) contains the desired dihydropyridine compound can be accomplished by cleaving the dihydropyridine compound from a small portion of the treated resins (if a cleavable linking arm is employed) and subjecting this product to conventional analysis, e.g., nuclear magnetic resonance spectroscopy (^{1}H, ^{13}C, etc.), high performance liquid chromatography, and the like. Alternatively, the reaction can be monitored by use of appropriate resins using gel-phase C^{13}-nuclear magnetic resonance spectroscopy.

While FIG. 2 illustrates formation of dihydropyridine 7 from a β-keto ester covalently attached to a solid support, it is understood, however, that aldehyde 4 could likewise be covalently attached to the solid support to form a covalently attached Knoevenagel condensation product.

Likewise, in FIG. 2, enamino compound 6 can be replaced by, for example, 6-aminouracil leads to the solid phase synthesis of pyrido[2,3-d]pyrimidine compounds.

Alternatively, FIG. 3 illustrates still another method for forming 1,4-dihydropyridine compounds wherein enamino compound 12 is covalently attached to the solid support and then subsequently reacted with either a Knoevenagel condensation product 13 or with β-keto ester, β-keto amide or β-diketone 14 and aldehyde 15 which, *in situ* forms a Knoevenagel condensation product. In either case, adduct 17 is believed to be formed. It being contemplated that any adduct 16 formed during reaction may be isomerized in the presence pyridine to adduct 17. Adduct 17, in the presence of a cleaving agent such as TFA undergoes cyclization and cleavage to provide for soluble 1,4-dihydropyridine compound 18.

Specifically, in FIG. 3, β-keto ester, β-keto amide or β-diketone 11 (Y and R^5 are as defined above) is contacted with a suitable resin 10 having a reactive amine functional group such as PAL resins or resins having an amino acid or peptide bound thereto (through the carboxyl group) under conditions suitable to covalently attach β-keto ester, β-keto amide or β-diketone 11 to resin 10 to provide for enamino compound 12. In this regard, β-keto ester, β-keto amide or β-diketone 11 serve as an enamino precursor compound insofar as upon contact with resin 10, these compounds are converted to enamino compounds.

The reaction is typically conducted in an inert diluent preferably under dehydrating conditions to effect formation of enamino compound 12. The inert diluent is not critical and preferred diluents include chloroform, dichloromethane, ethyl acetate, etc. and suitable dehydrating conditions include, for example, the use of molecular sieves (MS 4A) or the use of trimethyl orthoformate or tetramethyl orthosilicate. The reaction is

typically conducted at a temperature of from about 15° to 60°C and preferably at room temperature for a period of from about 24 to about 72 or more hours. In an optional embodiment, a protonating catalyst such as p-toluenesulfonic acid (TsOH) is employed at about from 0.1 to about 0.5 equivalents. The resulting enamino compound covalently attached to a solid support 12 can then be converted to soluble 1,4-dihydropyridine compounds 18 by one of two routes.

In one embodiment, solid phase enamino compound 12 is contacted in an inert diluent with at least a stoichiometric amount of Knoevenagel condensation product 13 (X, R^1 and R^6 are as defined above) in the presence of a base under conditions to effect formation of adduct 17. Because this embodiment employs only two reagents, this embodiment is sometimes referred to herein as the two component condensation.

In another embodiment, enamino compound 12 is contacted with β-keto ester, β-keto amide or β-diketone 14 (X and R^1 are as defined above) and aldehyde 15 (R^6 is as defined above) which, *in situ*, forms a Knoevenagel condensation product and then subsequently forms adduct 16. Because this embodiment employs three reagents, this embodiment is sometimes referred to herein as the three component condensation.

In either case, the presence of a suitable base permits isomerization of the unsaturation in adduct 16 to a position α to the keto group in adduct 17. Without being limited to any theory, such isomerization is believed to be necessary to effect nitrogen-carbon cyclocondensation rather than carbon-carbon cyclocondensation which results in formation of isomeric 2-amino-1,3-cyclohexadiene derivative. The particular base employed is not critical and suitable bases include pyridine, triethylamine, diisopropylethylamine, etc. Likewise, the particular inert diluent employed in either the two-component condensation or the three component

condensation reaction is not critical and suitable diluents include ethyl acetate, chloroform, toluene, benzene, dichloromethane, and the like. In a particularly preferred embodiment, the inert diluent is a weak base (e.g., pyridine).

Again, in either case, the reaction is typically conducted at from about 10° to about 80°C for a period of time to effect formation of adduct 17. Preferably, the reaction is complete within from about 12 to about 24 hours. Optionally, dehydrating conditions, as described above, are employed in this reaction.

When an aryl substituent is employed at the 4-position of the 1,4-dihydropyridines, the two component condensation procedure tolerates both donor, neutral and acceptor aryl substituents. However, the three component condensation procedure is best conducted with neutral and acceptor aryl substituents.

In a preferred embodiment, the solution phase components in either the two or three component reactions are used in excess to the solid phase component. Preferably the solution phase components are used from about a 5 to 50 fold excess relative to the solid phase component. Also, there is good tolerance for linear alkoxycarbonyl substituents at positions 3 and 5 and linear substituents at positions 2 and 6 of the dihydropyridines.

Adduct 17 is then converted to 1,4-dihydropyridine compound 18 by contact with a strong acid (e.g., 3% TFA in DCM) under an inert atmosphere such as argon. In FIG. 3, it is uncertain as to whether adduct 17 first cyclizes and then cleaves from the resin to form soluble 1,4-dihydropyridine compound 18 as shown in Route I of FIG. 3 or whether adduct 15 first cleaves from the resin and then cyclizes to form soluble 1.4-dihydropyridine compound 18 as shown in Route II of FIG. 3. In practice,

the particular order of reaction is believed to be dependent on factors such as the linking arm employed, the particular adduct contained on the resin and the cleavage conditions. In any event, a library of soluble 1,4-dihydropyridine compounds 18 is prepared.

Final cleavage and isolation of the 1,4-dihydropyridine compounds 18 should be performed under an inert atmosphere to avoid the conversion of readily oxidizable 1,4-dihydropyridines into pyridines. On the other hand, if the generation of a library of pyridine compounds is desired, oxidation of 1,4-dihydropyridine compounds to pyridine compounds provides a ready route to such libraries whether the library is a solid phase or solution library. In addition to exposure to air, other suitable oxidation conditions are well known in the art. One preferred set of oxidation conditions is illustrated in FIG. 2 wherein solid phase bound 1,4-dihydropyridine adduct 7 is oxidized to solid phase bound pyridine adduct 8 by reaction with ceric ammonium nitrate (CAN) in the presence of an inert diluent such as DMA at room temperature. The solid phase particle can be cleaved by treatment with a strong acid such as TFA to provide for soluble pyridine compound 8a. Freshly prepared CAN solution in DMA should be delivered immediately before an oxidation step to avoid the degradation of the oxidant in the organic solvent.

In view of the above, the choice of suitable reagents among the enamino compounds, the Knoevenagel condensation products and/or the β-keto esters, β-keto amide and β-diketones employed to prepared the 1,4-dihydropyridine compounds disclosed herein provides a facile means for preparing 1,4-dihydropyridine compounds having a variety of substituents at the 1, 2, 3, 4, 5 and 6 positions of the 1,4-dihydropyridine. Chemical derivation on the substituents so formed leads to still other substituents. For example, transesterification of carboxyl esters can provide for modification of the ester functionality. Moreover, oxidation of the 1,4-

dihydropyridine compounds provides for pyridine compounds.

Preferred substituents at the 1, 2, 3, 4, 5 and 6 positions of the 1,4-dihydropyridine and the pyridine compounds can be prepared via the methods described herein from starting materials which are either known *per se* in the art or which can be prepared by art recognized methods are described above.

Methods for Preparing 1,4-Dihydropyrimidine and Pyrimidine Compounds

Methods similar to those set forth above for preparing 1,4-dihydropyridine compounds can also be employed to prepare 1,4-dihydropyrimidine compounds with the exception that the enamino compound employed in the above reaction schemes is replaced by an amidine compound.

Solution phase synthesis of 1,4-dihydropyrimidine compounds is well known in the art.[18] Solid phase synthesis of 1,4-dihydropyrimidine compounds is achieved by covalent attachment of either the amidine compound or the Knoevenagel condensation product to a solid support. Solid phase Knoevenagel condensation products are described above whereas solid phase amidine compounds are prepared by reaction of an amino, hydroxyl or thiol functionalized solid support with, for example, known reagent 1-*H*-pyrazole-1-carboxamidine. Reaction of the functionalized solid supports with this reagent leads to displacement of the pyrazole group by the functional group.[20,21]

As with 1,4-dihydropyridine compounds, 1,4-dihydropyrimidine compounds are susceptible to oxidation to pyrimidine compounds and should be handled in an inert atmosphere. On the other hand,if the generation of a library of pyrimidine compounds is desired, oxidation of 1,4-dihydropyrimidine compounds to pyrimidine compounds provides a ready route to such libraries whether the library is a solid phase or solution

library. In addition to exposure to air, other suitable oxidation conditions are well known in the art. One preferred set of oxidation conditions is the reaction of solid phase bound 1,4-dihydropyrimidine adduct with ceric ammonium nitrate (CAN) in the presence of a diluent such as DMA at room temperature to provide for the solid phase bound pyrimidine adduct. The solid phase particle can be cleaved by treatment with a strong acid such as TFA to provide for soluble pyrimidine compounds.

In view of the above, the choice of suitable reagents among the amidine compounds, the Knoevenagel condensation products and/or the β-keto esters, β-keto amide and β-diketones employed to prepared the 1,4-dihydropyrimidine compounds disclosed herein provides a facile means for preparing 1,4-dihydropyrimidine compounds having a variety of substituents at the 1, 2, 4, 5 and 6 positions of the 1,4-dihydropyrimidine. Chemical derivation on the substituents so formed leads to still other substituents. For example, transesterification of carboxyl esters can provide for modification of the ester functionality. Moreover, oxidation of the 1,4-dihydropyrimidine compounds provides for pyrimidine compounds.

Preferred substituents at the 1, 2, 4, 5 and 6 positions of the 1,4-dihydropyrimidine and the pyrimidine compounds can be prepared via the methods described herein from starting materials which are either known *per se* in the art or which can be prepared by art recognized methods are described above.

Alternative Methods for Preparing Pyrimidine Compounds

Alternatively, solid phase pyrimidine compounds can be prepared by reaction of an amidine compounds with 1,3-dicarbonyl compounds such as β-keto esters, β-keto amides, β-diketones and the like at elevated temperatures (e.g., ~80°C) in an inert diluent such as dimethylformamide optionally using dehydrating conditions as described above wherein either

the 1,3-dicarbonyl compound or the amidine compound is covalently bound to a solid support.

As illustrated in FIG. 6, such alternative methods permit the formation of a library of pyrimidine compounds having a variety at substitutions 2, 4, 5 and 6 positions.

Accordingly, another method aspect of the invention is a method for preparing pyrimidine groups covalently attached to a solid support which are prepared by contacting a dicarbonyl compound selected from the group consisting of β-keto ester, a β-keto amide or a β-diketone with an amidine compound under conditions effective to provide for the pyrimidine group wherein the dicarbonyl compound or the amidine compound is covalently attached to a solid support.

The other methods described above can likewise be used to prepare libraries of pyrimidine groups covalently attached to solid supports merely be substituting a dicarbonyl compound selected from the group consisting of β-keto ester, a β-keto amide or a β-diketone for the Knoevengal condensation product in these methods.

Method for Producing Large Synthetic Libraries of Compounds

The above described synthetic methods can be incorporated into one or more reaction procedures in the stochastic methods described in International Patent Application Publication No. 93/06121 to prepare synthetic libraries of 1,4-dihydropyridine, pyridine, 1,4-dihydropyrimidine or pyrimidine compounds on solid supports. This application is incorporated herein by reference in its entirety. In such libraries, each solid support will preferably contain a single compound which compound is different to the compounds found on the other solid supports but each

compound will also comprise a 1,4-dihydropyridyl, pyridyl, 1,4-dihydropyrimidyl or pyrimidyl group.

It is understood, however, that the term "single compound" as used herein includes different regio and stereoisomers of that compound. In this regard, unsymmetric substitution at the 2,6 and/or 3,5 positions of the 1,4-dihydropyridine compounds generates a chiral center at the 4-position. In certain cases, individual isomers possess opposite actions on the calcium channel; one showing blocking activity and the other demonstrating activating activity.[22]

Also, the term "single compound" does not mean that only one copy of that compound is attached to each support. Rather, multiple copies of *that* compound can be included on the support.

In general, such methods can employ either a covalently bound Knoevenagel condensation product or a covalently bound enamino/amidine compound. When the Knoevenagel condensation product is covalently bound to the support, this method can comprise apportioning supports comprising a linking arm having a reactive amino or hydroxyl functionality into a plurality of reaction vessels, combining into each reaction vessel a different β-keto ester, β-keto amide or β-diketone such that the β-keto ester, β-keto amide or β-diketone becomes covalently attached to the linking arm of the supports through the amino or hydroxyl functionality, pooling the supports and then apportioning the supports among a plurality of reaction vessels, combining into each reaction vessel a different aldehyde under conditions wherein the β-keto ester, the β-keto amide or the β-diketone forms a Knoevenagel condensation product with the aldehyde, pooling the supports produced above and then apportioning the supports among a plurality of reaction vessels, combining into each reaction vessel a different enamino group or a different amidine group under conditions

wherein the Knoevenagel condensation product and the enamino or amidine group form an adduct, cyclizing the adduct to form a 1,4-dihydropyridine compound when an enamino group is employed and a 1,4-dihydro-pyrimidine compound when an amidine group is employed.

When the enamino/amidine compound is covalently bound to the support, this method can comprise apportioning supports comprising a linking arm having a reactive amino or hydroxyl functionality into a plurality of reaction vessels, combining into each reaction vessel a different enamino/amidine group (or enamino/amidine precursor group) such that the enamino/amidine group (or enamino/amidine precursor group) becomes covalently attached to the linking arm through the amino or hydroxyl functionality wherein, in the case of the enamino/amidine precursor groups, the attachment converts the enamino/amidine precursor group to an enamino group or amidine group, pooling the supports and then apportioning the supports among a plurality of reaction vessels, combining into each reaction vessel a different Knoevenagel condensation product under conditions wherein the Knoevenagel condensation product and the enamino/amidine group form an adduct, and cyclizing the adduct to form a 1,4-dihydropyridine compound when an enamino group or employed or a 1,4-dihydropyrimidine compound when an amidine group is employed.

Libraries of 1,4-dihydropyridine compounds and 1,4-dihydro-pyrimidine compounds can be converted to libraries of pyridine and pyrimidine compounds respectively by oxidation and the 1,4-dihydropyridine can be converted to libraries of piperidine compounds by reduction (see, e.g., example 65 below).

In the alternative methods for preparing pyrimidine compounds, solid phase libraries can employ either a covalently bound dicarbonyl compound or a covalently bound amidine compound. When the dicarbonyl compound is

covalently bound to the support, this method can comprise apportioning supports comprising a linking arm having a reactive amino or hydroxyl functionality into a plurality of reaction vessels, combining into each reaction vessel a different β-keto ester, β-keto amide or β-diketone or a different β-keto ester, β-keto amide or β-diketone precursor such that the β-keto ester, β-keto amide or β-diketone becomes covalently attached to the linking arm of the supports through the amino or hydroxyl functionality wherein, in the case of the β-keto ester, β-keto amide or β-diketone precursors, the attachment converts these precursor groups to a β-keto ester β-keto amide or β-diketone group respectively, pooling the supports and then apportioning the supports among a plurality of reaction vessels, combining into each reaction vessel a different amidine group under conditions wherein the dicarbonyl compound and the amidine group cyclize to form a pyrimidine compound.

When the amidine compound is covalently bound to the support, this method can comprise apportioning supports comprising a linking arm having a reactive amino or hydroxyl functionality into a plurality of reaction vessels, combining into each reaction vessel a different amidine group (or amidine precursor group) such that the amidine group (or amidine precursor group) becomes covalently attached to the linking arm through the amino or hydroxyl functionality wherein, in the case of the amidine precursor groups, the attachment converts the amidine precursor group to an amidine group, pooling the supports and then apportioning the supports among a plurality of reaction vessels, combining into each reaction vessel a different dicarbonyl compound selected from the group consisting of β-keto esters, β-keto amides and β-diketones under conditions wherein the Knoevenagel condensation product and the amidine group cycle to form a pyrimidine compound.

Preferably, the library will contain at least about 10 compounds, more preferably from about 10^2 to about 10^{10} compounds and still more preferably from about 10^3 to about 10^6 compounds.

In another preferred aspect of this embodiment, each solid support is tagged with an identifier tag that can be easily decoded to report the compounds formed on the solid support. The tag can be directly attached either to the solid support or the tag can be included on the compound itself. In this latter embodiment, cleavage of the compound from the solid support will still permit identification of the compound. Each of these embodiments is disclosed in International Patent Application Publication No. WO 93/06121. Alternatively, a portion of the same compounds attached to a single support is cleaved and subjected to mass spectroscopy, nuclear magnetic resonance spectroscopy and/or other forms of direct structural analysis so as to identify the compound on the support.
One preferred method for tagging employs a hard tagging scheme which is illustrated by Gallop, et al.[29]

Still another method for incorporating a tag with the solid support is disclosed in U.S. Patent Application Serial No. 08/146,886 and entitled "METHOD OF SYNTHESIZING DIVERSE COLLECTIONS OF COMPOUNDS" which application is incorporated herein by reference in its entirety.

In still another embodiment, the 1,4-dihydropyridine, the pyridine, the 1,4-dihydropyrimidine, or the pyrimidine groups can be incorporated into each compound in a library of different compounds all of which are covalently linked to the same solid support in the manner described in U.S. Patent No. 5,143,854. Such a library of different compounds can be simultaneously screened for receptor binding or some other activity. U.S. Patent No. 5,143,854 is incorporated herein by reference in its entirety.

Additionally, libraries of compounds attached to solid supports can be used for a variety of additional uses as set forth in International Patent Application Publication No. WO 93/06121.

Utility

The libraries of 1,4-dihydropyridine and 1,4-dihydropyrimidine compounds disclosed herein are useful in screening these compounds for activity as organic calcium channel modulators having therapeutic utility in the treatment of cardiac arrhythmias, hypertension, angina pectoris, vasospastic, supraventricular tachycardia, ventricular tachyarrhythmia, congestive heart failure, asthma, cerebral insufficiency and vasospams, and in the protection against ischemic heart damage.[4,5,8] . These libraries can also be employed to screen compounds for use as biological tools for studies of voltage-activated calcium channel structure and function and for use as liver protecting agents. Additionally, these libraries can be used to screen compounds for use in inhibiting platelet aggregation including, for example, platelet aggregation induced by PAF-acether (1-*O*-hexadecyl/octadecyl-2-*O*-acetyl-*sn*-glycero-3-phosphoryl-choline) and platelet aggregation induced by B16 amelanotic melanoma. Libraries of 14-dihydropyridines can further be screened for antioxidant, antitumor, antimutagenic, geroprotective, antiatherosclerotic, bronchodilating, antifungal, antiviral, antibacterial and antidiabetic activity.[27]

Libraries of pyridine compounds can be screened for inhibition of myeloperoxidase release from polymorphonuclear leukocytes (PMN) which, in turn, is theorized to modulate the tissue destructive nature of adult respiratory distress syndrome.[25] Pyridine and pyrimidine libraries can also be screened for anticonvulsant activity in mice[24]. Additionally, pyridine libraries can be screened for zinc chelating properties which can inhibit the binding of HIV-EP1 to NF-κB recognition sequence.[23]

Likewise, libraries of pyrimidine compounds can be screened for inhibiting human leukocyte elastase.

The following examples are set forth to illustrate the claimed invention and are not to be construed as a limitation thereof.

EXAMPLES

Unless otherwise stated, all temperatures are in degrees Celsius. Also, in these examples, unless otherwise defined below, the abbreviations employed have their generally accepted meaning:

	Ar	=	aromatic
	CAN	=	ceric ammonium nitrate
	^{13}C-NMR	=	carbon^{13} nuclear magnetic resonance
	d	=	doublet
	dd	=	doublet of doublets
	ddd	=	doublet of doublets of doublets
	DCM	=	dichloromethane
	DIEA	=	diisopropylethylamine
	DMA	=	N,N-dimethylacetamide
	DMAP	=	4-dimethylaminopyridine
	DMF	=	dimethylformamide
	EDAA	=	ethylene diamine acetate
	ESI	=	electron spray ionization
	FMOC	=	fluorenylmethyl oxycarbonyl
	g	=	gram
	HATU	=	[O-(7-azabenzotriazol-1-yl)]-1,1,3,3-tetramethyuronium hexafluorophosphate
	^{1}H-nmr	=	proton nuclear magnetic resonance
	HPLC	=	high performance liquid chromatography
	LDA	=	lithium diisopropylamide
	m	=	multiplet
	mg	=	milligram
	mL	=	milliliter
	mm	=	millimeter
	mmol	=	millimol
	MS	=	mass spectroscopy
	ppm	=	parts per million
	PyBrop	=	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
	RP HPLC	=	reverse phase high performance liquid chromatography
	RT	=	room temperature
	s	=	singlet
	t	=	triplet

TES	=	triethylsilane
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
TMOF	=	trimethylorthoformate
TMS	=	tetramethylsilane
μL	=	microliters
PAL resin	=	polystyrene resin functionalized with [5-(4-aminomethyl-3,5-dimethoxy)phenoxy]valeric acid
RINK resin	=	polystyrene resin functionalized with 4-[2',4'-dimethoxyphenyl)aminomethyl]phenol
TentaGel S RAM resin	=	polyethylene glycol resin functionalized with 4-[2',4'-dimethoxyphenyl)aminomethyl]phenol
WANG resin	=	polystyrene resins functionalized with p-benzyloxybenzyl alcohol

^{1}H- and ^{13}C-NMR spectra were recorded on Varian Gemini-400 spectrometer with TMS as internal standard. Mass-spectra were obtained on Finnigan TSQ-7000 instrument using ESI technique. HPLC analysis and purification were performed on Waters 717plus system using 5 μ Delta Pak 3.9 x 150 mm reverse phase column. All starting reagents were commercially available [e.g., Aldrich Chemical Company (Milwaukee, Wisconsin, USA), Fluka, (Buchs, Switzerland), Lancaster (Windham, New Hampshire, USA) and used without purification. Wang resin (loading 0.9 mmol/g), FMOC-protected Rink resin (loading 0.46 mmol/g) and PAL resin (loading 0.9 mmol/g) were obtained from Advanced Chemtech (Louisville, Kentucky, USA), and TentaGel S RAM resin (loading 0.24 mmol/g) was purchased from Rapp Polymere (Tübingen, Germany).

The general procedures set forth below illustrate methods generally employed to effect the desired reaction. Specific examples will recite any deviation from these general procedures.

Examples 1 and 2 illustrate the preparation of specific solid phase enamino compounds covalently bound to a solid support. Example 3

illustrates the solution phase synthesis of a Knoevenagel condensation product. Examples 4-47 illustrate the synthesis of numerous 1,4-dihydropyridine compounds via a solid phase enamino group. Examples 48 and 49 illustrate the preparation of libraries of soluble 1,4-dihydropyridine compounds via the methods illustrated in Examples 1 through 47. Examples 50-56 illustrate the preparation of specific solid phase Knoevenagel condensation products and subsequent conversion of these products to solid phase 1,4-dihydropyridine compounds and 1,4-dihydropyrimidine compounds. Examples 57-58 illustrate solid phase conversion of 1,4-dihydropyridine and 1,4-dihydropyrimidine compounds to pyridine and pyrimidine compounds respectively. Examples 59-65 illustrate particular embodiments of this invention.

General Procedure A - Preparation of N-Immobilized Enamino Esters

An appropriate FMOC-protected resin (0.5 g) is vortexed with 10% piperidine in DMF (5 mL) for 40 minutes. The resulting amine resin is filtered, washed with DMF (4 x 7 mL), MeOH (3 x 7 mL), $CHCl_3$ (3 x 7 mL), diethyl ether (7 mL), and dried in a vacuum dessicator (RT, 0.5 Torr). Resin thus obtained is vortexed with an appropriate β-keto ester (about 30 equivalents with respect to the loading of starting resin), and molecular sieves 4A (1 g) in DCM (4 mL) for 3 days at RT. The product is filtered, washed with $CHCl_3$ (3 x 7 mL), ethyl acetate (3 x 7 mL), diethyl ether (7 mL), and dried in a vacuum dessicator (RT, 0.5 Torr).

Example 1 -- Synthesis of N-Immobilized on PAL Resin $^{13}C_2$-2,4 Methyl Aminocrotonate

Following the procedure set forth above, C^{13} labeled (at the 2 and 4 positions) methyl aminocrotonate was immobilized onto PAL resin. Fast gel phase ^{13}C NMR in C_6D_6 gave the following peaks: (δ, ppm): 19.7 ($^{13}CH_3$), 82.6 ($^{13}CH=$).

Example 2 – Synthesis of N-Immobilized on RINK Resin $^{13}C_2$-2,4 Methyl Aminocrotonate

Following the procedure set forth above, C^{13} labeled (at the 2 position) 2,4 methyl aminocrotonate was immobilized onto RINK resin. Fast gel phase ^{13}C NMR[6] in C_6D_6 gave the following peaks (δ, ppm): 18.3 ($^{13}CH_3$), 83.4 ($^{13}CH=$).

Example 3 – Preparation of Methyl 2-(*p*-nitrobenzylidene)acetoacetate

Methyl acetoacetate (11.6 g, 0.1 mol) was combined with *p*-nitrobenzaldehyde (15.1 g, 0.1 mol) into a solvent mixture containing acetic acid (1.2 mL), benzene (50 mL) and piperidine (0.4 mL). The reaction mixture was refluxed under water removal conditions using a Dean-Stark trap for approximately 2 hours. The mixture was evaporated, dissolved in ethyl acetate (300 mL) and washed with 5% aqueous hydrochloric acid (2 X 100 mL), water (200 mL) and 5% sodium bicarbonate. The organic layer was dried ($MgSO_4$) and evaporated under vacuum to give 24.0 g of the title compound as a mixture of E and Z isomers in a ratio of about 3:1. ^1H-NMR ($CDCl_3$) (δ, ppm): 2.35 (s, Me, Z-isomer), 2.45 (s, Me, E-isomer), 3.83 (s, OMe, E-isomer), 3.87 (s, OMe, Z-isomer), 7.53-7.64 (m, Ar and CH of Z-isomer), 7.70 (s, CH of E-isomer), 8.20-8.25 (m, Ar).

General Procedure B - Solid Phase Preparation of 1,4-Dihydropyridine

Method A An appropriate resin-immobilized enamino ester (0.05 g) prepared in the manner described above and commercially available β-keto ester (1 mmol) [or β-diketone (1 mmol)] and a commercially available aldehyde (1 mmol) are combined with molecular sieves 4A (0.25 g) in dry pyridine (0.75 mL) and stirred at RT or 40°C under argon in a sealed amber vial for 24 hours (or as specified in Table 2 below). The resin is filtered, washed with methanol (4 x 7 mL) and then with ethyl

acetate (4 x 7 mL), and dried in a vacuum dessicator (RT, 0.5 Torr). The resulting resin is stirred under argon with 3% TFA in DCM (1 mL) for 60 minutes. Degassed acetonitrile (4 mL) is added, and the supernatant separated and quickly evaporated *in vacuo* with addition of toluene (2 mL) to ensure complete TFA removal. The crude products can be further purified by gradient RP HPLC (from 90% of the 0.1% TFA in water to 70% of the 0.1% TFA in acetonitrile over 60 minutes) using degassed solvents.

Method B The procedure of Method B is analogous to that of Method A, with the exception that a benzylidene β-keto ester (1 mmol) is employed instead of a mixture of β-keto ester and aldehyde.

Example 4 -- PAL Resin Supported Adduct 17 from Reaction of N-Immobilized $^{13}C_2$-2,4 Methyl Aminocrotonate with Methyl 2-(*p*-Nitrobenzylidene)acetoacetate

N-Immobilized $^{13}C_2$-2,4 methyl aminocrotonate, prepared as above, was reacted with methyl 2-(p-nitrobenzylidene)acetoacetate (prepared per Example 3 above) in the manner of Method B of General Procedure B above to provide for an adduct having the following analytical data: Fast gel phase ^{13}C NMR in C_6D_6 (δ, ppm): 15.3 ($^{13}CH_3$), 90.3 and 91.3 ($^{13}CH=$).

Example 5 -- RINK Resin Supported Adduct 17 from Reaction of N-Immobilized $^{13}C_2$-2,4 Methyl Aminocrotonate 2 with Methyl 2-(*p*-Nitrobenzylidene)acetoacetate

N-Immobilized $^{13}C_2$-2,4 methyl aminocrotonate, prepared as above, was reacted with methyl 2-(p-nitrobenzylidene)acetoacetate (prepared per Example 3 above) in the manner of Method B of General Procedure B above to provide for an adduct having the following analytical data: Fast

gel phase ^{13}C NMR in C_6D_6 (δ, ppm): 15.0 and 15.3 ($^{13}CH_3$), 92.0 and 92.9 ($^{13}CH=$). IR in KBr (ν, cm^{-1}): 1735 (CO_2Me), 1715 (CO).

Cleavage of the adducts from the resin is achieved in the manner described above for Methods A and B which cleaves the resin from the product and provides for soluble 1,4-dihydropyridine compounds.

Following the procedure of Examples 1-5 above, 1,4-dihydropyridines of Examples 6-47 were prepared.

Example 6 -- Synthesis of 4-(*o*-nitrophenyl)-2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridine

Prepared according to the Method A of General Procedure B above from an enamino compound N-tethered to Rink resin wherein the enamino compound was derived from methyl acetoacetate and then reacted with *o*-nitrobenzaldehyde and methyl acetoacetate. Yield 5.5 mg (70%). MS $(M+H)^+$ 347.1. ^1H NMR in $CDCl_3$ (δ, ppm): 2.35 (s, 6H, Me), 3.59 (s, 6H, OMe), 5.69 (s, 1H, 4-H), 5.72 (s, 1H, NH), 7.23-7.28 (m, 1H, Ar), 7.46 (ddd, 1 H, J=7.9, 7.1, and 1.3 Hz, Ar), 7.51 (dd, 1 H, J=8.0 and 1.6 Hz, Ar), 7.68 (dd, 1H, J=8.1 and 1.4 Hz, Ar).

Example 7 -- Synthesis of 4-(*m*-Nitrophenyl)-2,6-dimethyl-3-ethoxycarbonyl-5-methoxycarbonyl-1,4-dihydropyridine

Prepared according to the Method A of General Procedure B above from an enamino compound N-tethered to Rink resin wherein the enamino compound was derived from methyl acetoacetate and then reacted with *m*-nitrobenzaldehyde and ethyl acetoacetate. Yield 6.2 mg (75%). MS $(M+Na)^+$ 383.0. ^1H NMR in $CDCl_3$ (δ, ppm): 1.23 (t, 3H, J=7.2 Hz, $MeCH_2$), 2.37 (s, 3H, Me), 2.38 (s, 3H, Me), 3.65 (s, 3H, OMe), 4.10 (m, 2H, OCH_2), 5.10 (s, 1H, 4-H), 5.71 (s, 1H, NH), 7.38 (dd, 1H,

J=8.0 and 7.9 Hz, Ar), 7.65 (m, 1H, Ar), 8.02 (m, 1H, Ar), 8.12 (m, 1H, Ar).

Example 8 -- Synthesis of 4-(*m*-Nitrophenyl)-2,6-dimethyl-3-(2-methoxy)ethoxycarbonyl-5-isopropoxycarbonyl-1,4-dihydropyridine

Prepared according to the Method A of General Procedure B above from an enamino compound N-tethered to Rink resin wherein the enamino compound was derived from (2-methoxy)ethyl acetoacetate and then reacted with *m*-nitrobenzaldehyde and isopropyl acetoacetate. Yield 7.5 mg (78%). MS $(M+H)^+$ 418.9. ^1H NMR in $CDCl_3$ (δ, ppm): 1.09 (d, 3H, J=6.2 Hz, *Me*CH), 1.26 (d, 3H, J=6.2 Hz, *Me*CH), 2.36 (s, 6H, Me), 3.54 (m, 2H, CH_2), 4.17 (m, 2H, OCH_2), 4.93 (m, 1H, OCH), 5.09 (s, 1H, 4-H), 5.70 (s, 1H, NH), 7.39 (dd, 1H, J=7.9 and 7.8 Hz, Ar), 7.67 (dd, 1H, J=7.7 and 1.1 Hz, Ar), 8.01 (m, 1H, Ar), 8.13 (m, 1H, Ar).

Example 9 -- Synthesis of 4-(*p*-Nitrophenyl)-5-acetyl-2,6-dimethyl-3-methoxycarbonyl-1,4-dihydropyridine

Prepared according to Method A of General Procedure B above from an enamino compound N-tethered to Rink resin wherein the enamino compound was derived from methyl acetoacetate and then reacted with *p*-nitrobenzaldehyde and acetylacetone. Yield 5.7 mg (75%). MS $(M+H)^+$ 331.1. ^1H NMR in $CDCl_3$ (δ, ppm): 2.19 (s, 3H, Ac), 2.33 (s, 3H, Me), 2.38 (s, 3H, Me), 3.71 (s, 3H, OMe), 5.16 (s, 1H, 4-H), 5.73 (s, 1H, NH), 7.43 (d, 2H, J=6.8 Hz, Ar), 8.10 (d, 2H, J=6.8 Hz, Ar). ^{13}C NMR in $CDCl_3$ (δ, ppm): 19.7 (Me), 20.5 (Me), 29.9 (*Me*CO), 40.2 (C-4), 51.3 (OMe), 103.6 (C-3), 111.8 (C-5), 123.7 (2 C, Ar), 128.5 (2 C, Ar), 144.4 and 144.5 (C-2 and C-6), 153.6 (C-1' Ar), 167.4 (CO_2Me), 197.7 (*CO*Me).

Example 10 -- Synthesis of 4-(p-Nitrophenyl)-2,6-dimethyl-3-ethoxycarbonyl-5-methoxycarbonyl-1,4-dihydropyridine ($^{13}C_2$-3, 2-Me)

Prepared according to the Method B of General Procedure B above from an enamino compound N-tethered on a PAL resin wherein the enamino was derived from $^{13}C_2$-2,4 ethyl acetoacetate and then reacted with methyl 2-(*p*-nitrobenzylidene)acetoacetate. Yield 11.4 mg (70%). MS $(M+Na)^+$ 385.1. ^1H NMR in $CDCl_3$ (δ, ppm): 1.21 (t, 3H, J=7.1 Hz, *Me*CH_2), 2.36 (s, 3H, 6-Me), 2.36 (dd, 3H, J=129.7 and 3.5 Hz, $^{13}CH_3$), 3.62 (s, 3H, OMe), 4.09 (m, 2H, CH_2), 5.09 (d, 1H, J=7.4 Hz, 4-H), 5.65 (d, 1H, J=5.0 Hz, NH), 7.35 (d, 2H, J=8.7 Hz, Ar), 8.08 (d, 2H, J=8.7 Hz, Ar). Fast ^{13}C NMR in $CDCl_3$ (δ, ppm): 19.7 ($^{13}CH_3$), 103.3 (3-^{13}C).

Example 11 -- Synthesis of 4-(*p*-Nitrophenyl)-6-ethyl-2-phenyl-3-ethoxycarbonyl-5-methoxy-carbonyl-1,4-dihydropyridine

Prepared according to Method A of General Procedure B above from an enamino compound N-tethered to Rink resin wherein the enamino compound was derived from methyl propionylacetate and then reacted with p-nitrobenzaldehyde and ethyl benzoylacetate. Yield 7.0 mg (70%). MS $(M+H)^+$ 437.1. ^1H NMR in $CDCl_3$ (δ, ppm): 0.83 (t, 3H, J=7.2 Hz, *Me*CH_2), 1.24 (t, 3H, *Me*CH_2O), 2.68 (m, 1H, CH_2), 2.90 (m, 1H, CH_2), 3.67 (s, 3H, OMe), 3.83 (m, 2H, CH_2O), 5.21 (s, 1H, 4-H), 5.89 (d, 1H, NH), 7.27-7.73 (m, 2H, Ph), 7.38-7.46 (m, 3H, Ph), 7.51 (d, 2H, J=8.7 Hz, Ar), 8.14 (d, 2H, J=8.7 Hz, Ar). ^{13}C NMR in $CDCl_3$ (δ, ppm): 12.8 (Me), 13.6 (Me), 26.0 (CH_2), 40.1 (4-C), 51.3 (MeO), 60.0 (CH_2O), 102.3 and 102.4 (3-C, 5-C), 123.6, 127.9, 128.5, 128.6, 129.5, 136.4, 146.4, 150.6 (^{13}C, Ar, 2-C, and 6-C), 154.6 (C-1' of 4-$O_2NC_6H_4$), 167.0 and 167.2 (*CO*$_2$Me and *CO*$_2$Et).

Example 12 – Synthesis of 4-(*p*-Cyanophenyl)-2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridine

Prepared according to Method A of General Procedure B above from an enamino compound N-tethered to Rink resin wherein the enamino compound was derived from methyl acetoacetate which is then reacted with *p*-cyanobenzaldehyde and methyl acetoacetate. Yield 5.9 mg (74%). MS $(M+H)^+$ 348.9. ^1H NMR in $CDCl_3$ (δ, ppm): 2.35 (s, 3H, Me), 3.64 (s, 3H, OMe), 5.04 (s, 1H, 4-H), 5.68 (s, 1H, NH), 7.37 (d, 2H, J=8.5 Hz, Ar), 7.51 (d, 2 H, J=8.5 Hz, Ar).

Example 13 – Synthesis of 4-Phenyl-2,6-dimethyl-3-allyloxycarbonyl-5-methoxycarbonyl-1,4-dihydropyridine

Prepared according to Method B of General Procedure B above from an enamino compound N-tethered to Rink resin wherein the enamino compound was derived from methyl acetoacetate and then reacted with allyl (2-benzylidene)acetoacetate. Yield 5.4 mg (72%). MS $(M+H)^+$ 328.1. ^1H NMR in $CDCl_3$ (δ, ppm): 1.60 (s, 3H, Me), 2.05 (s, 3H, Me), 3.64 (s, 3H, MeO), 4.54 (m, 2H, CH_2), 5.03 (s, 1H, 4-H), 5.13-5.21 (m, 2H, CH_2=), 5.67 (s, 1H, NH), 5.83-5.93 (m, 1H, CH=), 7.11-7.28 (m, 5H, Ar). ^{13}C NMR in $CDCl_3$ (δ, ppm): 19.9 (Me), 20.0 (Me), 39.6 (C-4), 51.2 (MeO), 64.8 (CH_2O), 104.1 and 104.3 (3-C and 5-C), 117.6, 126.4, 127.9, 128.0, 128.2, 133.0 (C-1′ Ph), 144.3, 144.6, 147.7, 167.4 and 168.2 (CO_2Me and CO_2All).

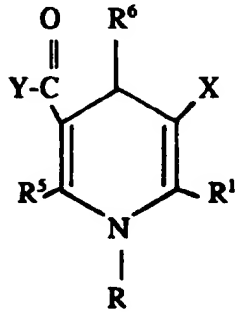
Example 14 – Synthesis of 4-(Pyridin-4-yl)-2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridine

Prepared according to Method A of General Procedure B above from an enamino compound N-tethered to Rink resin wherein the enamino compound was derived from methyl acetoacetate which was then reacted with 4-pyridinecarboxaldehyde and methyl acetoacetate. Yield 5.2 mg (75%). MS $(M+H)^+$ 302.5. ^1H NMR in $CDCl_3$ (δ, ppm): 2.37 (s, 3H,

Me), 3.65 (s, 3H, OMe), 5.23 (s, 1H, 4-H), 6.76 (s, 1H, NH), 7.85 (m, 2H, Py), 8.65 (m, 2H, Py). ^{13}C NMR in $CDCl_3$ (δ, ppm): 19.4 (Me), 41.09 (C-4), 51.5 (MeO), 100.7 (3-C and 5-C), 126.2, 140.8, 147.1, 166.9 and 167.0 (2 CO_2Me).

Examples 15-47 – Synthesis of 1,4-Dihydropyridines

Following the procedures set forth above, 1,4-dihydropyridine compounds of the formula



were prepared as set forth in Table 2 below. This table summarizes the method employed (i.e., either Method A or Method B of General Procedure B above), the reaction conditions and the purity of the resulting product.

TABLE 2

Entry #	Resin[a]	R^6	R^5	-OY (Y=)	R_1	C(O)X (X=)	Method/Reaction Conditions	Purity[b] %
15	PAL	o-$O_2NC_6H_4$	Me	Me	Me	OMe	B/Py, r.t., 48 h	80[c]
16	PAL	p-$O_2NC_6H_4$	Me	Me	Me	OMe	A/Py, r.t., 48 h	70
17	PAL	p-$O_2NC_6H_4$	Et	Me	Me	OMe	B/Py, r.t., 48 h	85
18	PAL	p-$O_2NC_6H_4$	Me	Me	Me	OMe	B/Py, 60 °C, 18 h	80
19	PAL	Ph	Me	Me	Me	OAll	B/Py, r.t., 48 h	65
20	Rink	Ph	Me	Me	Me	OAll	B/Py, r.t., 48 h	80
21	Rink	Ph	Me	All	Me	OAll	A/Py, 45 °C, 13 h	90
22	Rink	Ph	Me	Et	Me	OAll	B/Py, r.t., 48 h	54
23	Rink	Ph	Me	Me	Me	OAll	A/Py, r.t., 40 h	80
24	Rink	Ph	Me	Me	Me	OAll	A/Py, 60 °C, 17 h	75
25	Rink	4-Pyridyl	Me	Me	Me	OMe	A/Py, 60 °C, 17 h	75
26	Rink	p-NCC_6H_4	Me	Me	Me	OMe	A/Py, r.t., 34 h	85
27	Rink	Ph	Me	Bn	Me	OAll	A/Py, 45 °C,13 h	92
28	Rink	p-ClC_6H_4	Me	Me	Me	OBn	A/Py, r.t., 72 h	70
29	Rink	p-ClC_6H_4	Et	Me	Et	OMe	A/Py, 60 °C, 23 h	55
30	Rink	p-$MeOC_6H_4$	Me	Me	Me	OMe	A/Py, 60 °C, 23 h	70
31	Rink	1-naphthyl	Me	Me	Me	O^{t}Bu	A/Py, r.t., 6 d	30
32	Rink	1-naphthyl	Me	Me	Me	OMe	A/Py, 60 °C, 24 h	60
33	Rink	p-$O_2NC_6H_4$	Me	Me	Me	OMe	A/Py, 60 °C, 34 h	75
34	Rink	m-$O_2NC_6H_4$	Me	Me	Me	OEt	A/Py, r.t., 19 h	78[d]
35	Rink	p-$O_2NC_6H_4$	Et	Me	Ph	OEt	A/Py, 60 °C, 23 h	80
36	Rink	p-$O_2NC_6H_4$	Me	Me	Ph	OEt	A/Py, 60 °C, 21 h	90
37	Rink	p-$O_2NC_6H_4$	Me	Me	Me	OEt	A/Py, r.t., 34 h	78
38	Rink	o-$O_2NC_6H_4$	Me	Me	Me	OMe	A/Py, r.t., 72 h	79[c]
39	Rink	o-$O_2NC_6H_4$	Me	Me	Me	OMe	B/Py, r.t., 38 h	85[c]
40	Rink	p-$O_2NC_6H_4$	Me	^{t}Bu	Me	OMe	A/Py, r.t., 72 h	73
41	Rink	p-$O_2NC_6H_4$	Et	Me	Me	OMe	B/Py, r.t., 72 h	83
42	Rink	o-$O_2NC_6H_4$	Me	Me	Me	OBn	A/Py, 45 °C,13 h	82
43	Rink	o-$O_2NC_6H_4$	Me	Me	Me	OAll	A/Py, 45 °C, 13 h	82
44	Rink	m-$O_2NC_6H_4$	Me	$(CH_2)_2OMe$	Me	O^{i}Pr	A/Py, r.t., 72 h	90[e]
45	TG S RAM[f]	m-$O_2NC_6H_4$	Me	$(CH_2)_2OMe$	Me	O^{i}Pr	A/Py, r.t., 72 h	63[e]
46	Rink	p-$O_2NC_6H_4$	Me	Me	Me	Me	A/Py, 60 °C, 21 h	73
47	Rink	p-O2NC6H4	Me	Me	Me (Ph)	Ph (Me)	A/Py, 60 °C, 21 h	75[g]

Notes: [a]Compound were cleaved from PAL resin with 95% TFA/THF, and with 3 %TFA/DCM in all other cases. [b]As determined by HPLC. [c]Nifedipine. [d]Nitrendipine. [e]Nimodipine. [f]TentaGel S RAM resin (Rapp Polymere). [g]For mixture of two regioisomers in ratio ca. 1.3:1.

FIG. 7 illustrates an alternative synthesis for 1,4-dihydropyridines starting with an amino acid bound to a resin via the carboxyl group. The synthesis otherwise follows that set forth above. In this synthesis, the dihydropyridines can be made on a solid support via three types of readily available building blocks: amino acids, aldehydes and enamines. Thus, readily assessible acyl Meldrum's acids can be employed as diverse diketene synthones for generation of keto amides at the first step of the synthetic scheme.

Example 48 -- Synthesis of a 9 Member Library of Soluble 1,4-Dihydropyridine Compounds Via Solid Supports

A nine member library of 1,4-dihydropyridine compounds was prepared as shown in FIG. 5. Specifically, the FMOC protecting group was removed from FMOC-NH-RINK resin by treatment with 10% piperidine in DMF and washed with DMF (4 x 7 mL), methanol (3 x 7 mL), $CHCl_3$ (3 x 7 mL), diethyl ether (7 mL), and dried under vacuum. The resulting resin was split into three groups. The first group was contacted with an excess of methyl acetoacetate (about 30 equivalents) in DCM (optionally over molecular sieves (MS)) for about 48 hours at RT to provide for a first enamino compound covalently bound to a solid support as described above.

The second group was contacted with allyl acetoacetate in the manner described above to provide for a second enamino compound covalently bound to a solid support.

The third group was contacted with benzyl acetoacetate in the manner described above to provide for a third enamino compound covalently bound to a solid support.

The resins were then pooled and split into three additional groups wherein each group was treated with a different Knoevenagel condensation product in the manner described in FIG. 5 and then the solid support was removed by treatment with 3% TFA/THF in argon to provide for the nine member library of soluble 1,4-dihydropyridine compounds.

Example 49 -- Synthesis of a 100 Member Library of Soluble 1,4-dihydropyridine Compounds via Solid Supports

A library of 1,4-dihydropyridine compounds, 100 members, was prepared as follows:

Ten different enamino esters immobilized on Rink or TentaGel RAM resins were prepared separately as described above from the corresponding amine resin with each of the following keto esters: methyl acetoacetate, ethyl acetoacetate, isopropyl acetoacetate, t-butyl acetoacetate, methyl propionylacetate, i-butyl acetoacetate, allyl acetoacetate, benzyl acetoacetate, (2-methoxy)ethyl acetoacetate, and methyl (4-methoxy)acetoacetate.

The N-tethered enamino esters thus prepared (0.4 g of each resin) were pooled and then split in 10 portions. Every pool of immobilized enamino esters (0.4 g each) was reacted as described above with methyl acetoacetate and one of the following aldehydes: benzaldehyde, 4-chlorobenzaldehyde, 2-fluorobenzaldehyde, 2-trifluoromethylbenzaldehyde, 4-cyanobenzaldehyde, 4-nitrobenzaldehyde, 2-nitrobenzaldehyde, 4-pyridinecarboxaldehyde, 2-pyridinecarboxaldehyde, or 3-thiophene-carboxaldehyde, at 40°C over 24 hours. The resulting resins were cleaved under argon atmosphere with 3% TFA in dichloromethane (8 mL) for 60 minutes. Degassed acetonitrile (12 mL) was added, and the supernatant separated and quickly evaporated *in vacuo* with addition of toluene (4 mL) to ensure TFA removal. The resulted oily mixtures of 1,4-dihydro-

pyridines (ten subsets containing ten 1,4-dihydropyridines each) was further dried *in vacuo*, and stored at -15°C.

Screening of the 10 pools for calcium blockade activity using a cortex membrane binding assay[28] identified two pools derived from *ortho*-nitrobenzaldehyde and *ortho*-fluorobenzaldehyde respectively as the most active pools. Deconvolution via parallel synthesis of individual pool members was preformed and rough IC_{50} estimations made using the crude, unpurified samples. Compounds of interest were purified and Nifedipine and its closely related ethyl ester analog identified as active compounds. A better spread of activity was realized with the *ortho*-fluorobenzaldehyde pool.

The table below recites preferred compounds found from this library where each of R, R^1, R^5, R^6, X and Y are as defined above.

R	R^1	R^5	R^6	X	Y
H	$-CH_3$	$-CH_3$	*ortho*-NO_2-ϕ	$-C(O)OCH_2$-ϕ	CH_3O-
H	$-CH_3$	$-CH_3$	*ortho*-fluoro-ϕ	$-C(O)OCH(CH_3)_2$	CH_3O-
H	$-CH_3$	$-CH_3$	*ortho*-fluoro-ϕ	$-C(O)OCH_2$-ϕ	CH_3O-
H	$-CH_3$	$-CH_3$	*ortho*-NO_2-ϕ	$-C(O)OCH_3$	CH_3O-
H	$-CH_3$	$-CH_3$	*ortho*-NO_2-ϕ	$-C(O)OCH_2CH_3$	CH_3O-

Each of the above compounds has an IC_{50} of less than 100 nM in the described assay.

General Procedure C - Preparation of Immobilized β-Keto Esters, β-Keto Amides or β-Diketones

Method A

Diketene (13.0 mmol, 1.0 mL) is added dropwise with stirring at -55°C to an appropriate alcohol or amine resin (2.7 mmol) and DMAP (for reaction with alcohol resin; 0.04 mmol, 5 mg) in dichloromethane (20 mL). The mixture is allowed to warm up to RT over about 16 hours (for alcohol resin) or quenched with methanol after 2 hours at about -55°C (for amine resin; negative Kaiser test) and the resulting resin is filtered, washed with chloroform (5 x 7 mL) and dried under vacuum (RT, 0.5 Torr, 5 hours).

Method B

A mixture of alcohol resin (0.06 mmol) and an appropriate t-butyl keto ester (12.1 mmol) in toluene (10 mL) is stirred under gentle reflux for 2 hours followed by slow distillation of the resulting t-butanol over about 45 minutes (t-butanol distills with the toluene). The resulting resin is filtered, washed with chloroform (5 x 7 mL) and diethyl ether (3 x 7 mL), and dried in vacuum (RT, 0.5 Torr, 5 hours).

It is noted that the *t*-butyl esters can be prepared via transesterification techniques from other known esters using techniques well known in the art.

Method C

This method employs acyl Meldrum's acids. Specifically, a mixture of alcohol resin (0.1 mmol) and an appropriate acyl Meldrum's acid (2 mmol; freshly prepared reagents give better results) in toluene (1.5 mL; in a closed screw-cap vial) is stirred at 60°C (gives cleaner products than 80°C) for 15-18 hours. The resulting resin is filtered, washed intermittently with methanol (4 x 5 mL) and DCM (4 x 5 mL), and dried in vacuum (room temperature, 0.5 Torr, 5 hours).

Other methods for preparing immobilized β-keto esters, β-keto amides and β-diketones are set forth in Table I above.

Still another method for preparing immobilized keto esters are set forth in FIG. 9 which illustrates a synthetic scheme in which Wang resin is first acetylated via either acetic anhydride or acetyl chloride to provide for resin bound acetate. Reaction with LDA at -78°C in THF followed by reaction with a Weinreb amide. This reaction is generally conducted as follows. 1.5 M LDA in cyclohexane (0.5 mL, 0.75 mmol) is added dropwise with stirring at -78°C to an appropriate acetoxy alcohol resin (0.1 mmol) in THF (1 mL), and the mixture stirred at this temperature for 1 hour. An appropriate Weinreb amide (0.85 mmol) in THF (0.5 mL) is added dropwise with stirring, and the mixture allowed to warm up to room temperature overnight. The resulting resin is filtered, washed with methanol (2 x 5 mL), 5% acetic acid and 5% water in methanol (2 x 5 mL), methanol, DCM (liberally), and then dried under vacuum (room temperature, 0.5 Torr, 5 hours).

General Procedure D - Preparation of Immobilized Benzylidene β-Keto Esters, β-Keto Amides, or β-Diketones (Knoevenagel Condensation Products)

An appropriate β-keto ester, β-keto amide or β-diketone resin (0.63 mmol), aldehyde (5 mmol) and piperidine (0.06 mL, 0.6 mmol) in benzene (2 mL) and isopropanol (4 mL) are stirred with molecular sieves 4A (1.0 g) at 60°C for 24 hours. The resulting resin is filtered, washed with chloroform (5 x 7 mL) and diethyl ether (3 x 7 mL) and then dried under vacuum (RT, 0.5 Torr, 5 hours).

General Procedure E - Preparation of Side Chain Immobilized 1,4-Dihydropyridine and 1,4-Dihydropyrimidine Compounds

An immobilized benzylidene β-keto ester, β-keto amide or β-diketone (0.13 mmol) and a soluble enamino compound (4 mmol) are combined in methanol (3 mL) with DMF (0.3 mL) (for the preparation of 1,4-dihydropyridines), or amidine derivative (e.g., 2-methyl-2-

thiopsudourea sulfate, 4 mmol) in DMF (3-5 mL) containing base, such as sodium acetate, sodium carbonate, or DBU (0.1-0.2 mmol) (for preparation of 1,4-dihydropyrimidines). The resulting solution is stirred in the presence of molecular sieves 4A (0.36 g) in a sealed amber vial for 6-24 hours at 40°-90°C. The resulting resin is filtered, washed with methanol (5 x 7 mL), chloroform (5 x 7 mL) and diethyl ether (3 x 7 mL), and dried under vacuum (RT, 0.5 Torr, 5 hours).

General Procedure F - Preparation of Side Chain Immobilized Pyridines and 3-Pyridinecarboxylic Acid Derivatives

Ceric ammonium nitrate (0.055 g, 0.1 mmol) in DMA (1.5 mL) is added to an appropriate side chain immobilized dihydropyridine (0.13 mmol) and the mixture is vortexed at RT for 15 minutes. The resulting resin is filtered, washed with methanol (5 x 7 mL), ethyl acetate (3 x 7 mL), and dried under vacuum (RT, 0.5 Torr, 5 hours). The side chain immobilized pyridines thus obtained can be cleaved from the solid support using trifluoroacetic acid-based solutions or photolysis depending, of course, on the structure of the linking arm employed, to afford the corresponding 3-pyridinecarboxylic acid derivatives.

Example 50 -- Solid-Phase Synthesis of Acetoacetate to TentaGel S PHB Resin

TentaGel S PHB resin and t-butyl acetoacetate were combined in the manner of Method B of General Procedure C to provide for resin bound acetoacetate (loading capacity of 0.2 mmol/g of resin).

Example 51 -- Preparation of Knoevenagel Condensation Product Covalently Bound to a TentaGel S PHB Resin

Resin bound acetoacetate prepared in Example 50 was combined with *p*-nitrobenzaldehyde in a manner silimar to that described above in

General Procedure D to provide for the immobilized Knoevenagel Condensation product thereof.

Example 52 -- Preparation of TentaGel Resin Immobilized 4-(*p*-Nitrophenyl)-2,6-dimethyl-3-(resin)-oxycarbonyl-5-methoxycarbonylpyridine

Solid phase Knoevenagel condensation product prepared in Example 51 above was combined with methyl aminocrotonate in the manner described above in General Procedure E to provide for the title compound covalently attached to the solid support.

The title compound covalently attached to TentaGel S PHB resin decomposes if cleavage of this compound is attempted via conventional cleavage conditions, e.g., 95% TFA. It has been found that decomposition is due to the fact that the 5-carboxyl group resulting from cleavage results in an acid unstable product. Accordingly, for the purposes of this invention, TentaGel S PHB resin provides for a non-cleavable linking arm to the solid support when employed with 1,4-dihydropyridine compounds bound via a 3 or 5 carboxyl ester.

It is understood, however, that the TentaGel S PHB resin can be replace with cleavable resins such as those which possess a photo labile group. See, for example, U.S. Patent No. 5,143,854 as well as Jacobs, et al., *Combinatorial Chemistry - Application of Light-directed Chemical Synthesis*, Trends in Biotechnology, 12(1):19-26 (1994) and Fodor, et al., *Light-Directed Spatially Addressable Parallel Chemical Synthesis*, Science, 251:767-773 (1991) all of which are incorporated herein by reference in their entirety. When a photolabile linker is employed in conjunction with the synthesis of dihydropyridines, an oxygen-free atmosphere or the use of radical scavengers might be necessary and, in any event, no ortho-phenyl dihydropyridines can be obtained under these conditions.

Examples 53-56 below are illustrated in FIG. 2.

Example 53 -- Wang Resin Supported 2-Benzylidene ^{13}CH Acetoacetate

Wang Resin supported acetoacetated, prepared in a manner similar to Methods A or B of General Procedure C using Wang alcohol resin and diketene or t-butyl acetoacetate, was combined with (^{13}CHO)-labeled benzaldehyde in the manner of General Procedure D to provide for the title compound. Fast gel phase ^{13}C-NMR in C_6D_6 (δ, ppm): 141.0 (^{13}CH=).

Example 54 -- Wang Resin Immobilized 4-Phenyl-2,6-dimethyl-3-(resin)-oxycarbonyl-5-methoxycarbonyl-1,4-dihydropyridine (^{13}C-4)

Wang resin 2-benzylidine ^{13}CH acetoacetate prepared in the manner of Example 53 above was combined with methyl aminocrotonate (reaction time 24 hours at 80°C) in the manner of General Procedure E to provide for the title compound covalently attached to the solid support. Fast gel phase ^{13}C-NMR in C_6D_6 (δ, ppm): 40.2 (^{13}C-4).

Example 55 -- Preparation of Wang Resin Immobilized 4-Phenyl-2,6-dimethyl-3-(resin)oxycarbonyl-5-methoxycarbonyl-pyridine (^{13}C-4)

The compound prepared in Example 54 and ceric ammonium nitrate were combined in the manner of General Procedure F to provide for the title compound. Fast gel phase ^{13}C NMR in C_6D_6 (δ, ppm): 145.2 (^{13}C-4).

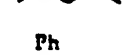
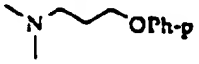
Example 56 -- Preparation of 4-Phenyl-2,6-Dimethyl-5-methoxy-carbonyl-3-pyridinecarboxylic acid (^{13}C-4)

The resin of Example 55 above was cleaved by treatment with 90% aqueous trifluoroacetic acid (0.2 mL, 45 minutes). The resulting supernatant was lyophilized with water (2 mL) to afford the title

compound. HPLC purity >85%. MS (M+H)$^+$ 287.0. ^{1}H NMR in $CDCl_3$ (δ, ppm): 2.70 (s, 3H, Me), 2.79 (s, 3H, Me), 3.58 (s, 3H, OMe), 7.23-7.53 (m, 5H, Ph).

The table below illustrates the different nicotinic acids prepared. It should be noted that synthesis with branched aliphatic aldehydes has been accomplished by dealkylation of the final product with TFA at the cleavage stage. Thus, dealkylated nicotinic acid was a sole product in conversions with isobutyraldehyde or diphenylacetaldehyde, and the predominant product in the synthesis with cyclohexanecarboxaldehyde. Subsequent syntheses utilizing the super acid labile Sasrin resin instead of the Wang support cleavage conditions (1% TFA in DCM) did not completely prevent the dealkylation, although the extent of this reaction did decrease. If necessary, this reaction may be avoided by the use of, for example, photocleavable linkers.

Solid-Phase Synthesis of Functionalized Nicotinic Acids

Entry #	R_1	R_2	R_3	HPLC product purity,[a] %	MS
1	Ph(C^{13})	MeO	Me	80	O'K
2	Ph(C^{13})	^{i}PrO	Me	95	O'K
3	p-HOOCPh	MeO	Me	99	O'K
4	o-FPh	MeO	Me	98	O'K
5	2-naphthyl	MeO	Me	98	O'K
6	4-Py	^{i}PrO	Me	81	O'K
7	m-O_2NPh	MeO	Me	95	O'K
8	p-MeOPh	^{i}PrO	Me	90	O'K
9[b]	n-Hex	MeO	Me	90	O'K
10[b]		MeO	Me	70	O'K[c]
11[b]	Ph	MeO	Me	90	O'K
12[b]		MeO	Me	70	O'K[d]
13[b]	Ph	Me	Me	90	O'K
14[b]	Ph	$CH_2CMe_2CH_2$		90	O'K

Notes: [a]Detection at 220 nm. [d]Dealkylation product's ion $[M - R_1 + 2H]^+$ was also detected.

The synthesis of 1,4-dihydropyrimidines attached to solid supports is illustrated in FIG. 4 and exemplified in Example 57 below:

Example 57 -- Preparation of solid phase 1,4-Dihydro-2-thiomethyl-6-methyl-4-[2-nitrophenyl]-5-pyrimidinecarboxylic Acid, Methyl Ester

Knoevenagel Condensation product (0.05 g) prepared as in Example 51 above is combined with commercially available 2-methyl-2-thio-pseudourea sulfate and sodium acetate in DMF in the manner of Atwal et al.[18], to provide for the title compound covalently attached to a solid support.

General Procedure G - Preparation of Immobilized Guanidines

An appropriate commercial Fmoc-protected amine resin (about 0.09 mmol) is swollen in DMF/DCM (1:1, 3 mL) for 10 minutes, washed with DMF (3 mL), deprotected with 20% piperdine in DMF (3 mL) for 20 minutes, and washed again with DMF (3 x 3 mL). It is then coupled with an apropriate Fmoc-protected amino acid (1.2 mmol) with HATU (5.4 mmol, 2.05 g) and DIEA (10.8 mmol, 1.88 mL) in DMF (15 mL) for 0.5 to 4 hours (until negative Kaiser test) using agitation under nitrogen. Resin is washed with DMF (3 x 5 mL), THF (3 x 5 mL), and acetylated with Ac_2O/lutidine/THF (1 mL) and N-methylimidazole/THF (1 mL) for 10 minutes (reagents available from Applied Biosystems, Foster City, California, USA). When desired [for the preparation of immobilized peptides with the terminal gluandidino and (un)substituted pyrimidyl groups], the deprotection/coupling/acetylation cycle is repeated as above for each of the next amino acid. The resin is then deprotected with 20% piperidine in DMF as above, washed with DMF (4 x 5 mL), ethyl acetate (4 x 5 mL) and dried under vacuum (RT, 0.5 Torr, 5 hours). The amine (or peptide) resin thus obtained (0.3 mmol) is stirred with 1H-pyrazole-1-carboxamidine (2.76 mmol, 0.405 g) and DIEA (3.13 mmol, 0.545 mL) in

DMF (4 x 5 mL), ethyl acetate (4 x 5 mL) and dried under vacuum (RT, 0.5 Torr, 5 hours).

General Procedure H - Solid Phase Preparation of Immobilized Pyrimidine Derivatives from Tethered Guanidines

The guanidine resin (0.03 mmol) in DMF (1 mL) or pyridine (1 mL) is stirred at 20°C to 80°C with an appropriate β-diketone (1 mmol, for preparation of pyrimidines) or benzylidene β-keto ester, β-keto amide or β-diketone (1 mmol, for the preparation of 1,4-dihydropyrimidines) and dehydrating agent [e.g., molecular sieves 4A, (0.16 g) or trimethylorthoformate or tetramethylorthosilicate (0.1-1 mmol)] for 6 to 24 hours. The resulting resin is washed with DMF (4 x 5 mL), ethyl acetate (4 x 5 mL) and dried under vacuum (RT, 0.5 Torr, 5 hours). The immobilized pyrimidines or 1,4-dihydropyrimidines thus obtained can be cleaved from the solid support using trifluoroacetic acid-based solvents or photolysis, to afford the corresponding pyrimidines or 1,4-dihydropyrimidines depending upon the linking arm employed.

Example 58 -- Rink Resin Supported Guanidineacetamide

The resin employed was glycine tethered through the carboxyl group to Rink resin. This resin was treated in the manner of General Procedure G over a reaction time of 26 hours to provide for the title compound. A portion of the resin was cleaved with 70% aqueous trifluoroacetic acid (0.8 mL) for 1.5 hours and the supernatant was lyophilized with water (2 mL) to afford guanidineacetamide (TFA salt) as a white powder. MS $(M+H)^+$ 116.7. ^{1}H-NMR in D_2O (δ, ppm): 3.99 (s, 2H, CH_2).

Example 59 -- Solid Phase Preparation of 2-(Amid methyl)amino-4,6-dimethylpyrimidine

The resin of Example 58 was combined with acetylacetone in the

manner of General Procedure H using molecular sieves 4A as the dehydrating agent over a reaction time of 15 hours to provide for the title compound. A portion of the resulting resin (0.05 g) was cleaved with 10% TFA/DCM (0.7 mL) for 1 hour. Resin was filtered off, and the filtrate evaporated under vacuum to afford the 2-(amidomethyl)amino-4,6-dimethylpyrimidine. MS $(M+H)^+$ 180.9 ^{1}H-NMR in $CDCl_3$ (δ, ppm): 2.53 (s, 6H, 2 Me), 4.31 (s, 2H, CH_2), 6.40 (br, s, 1H, NH, exchangeable), 6.58 [br, s, 2H, CH and NH (exchangeable NH)], 10.35 (br. s, 1H, NH).

Example 60 -- Solid Phase Preparation of 2-(Amidomethyl)amino-4-Trifluoromethyl-6-Phenylpyrimdine

The resin of Example 58 was combined with 4,4,4-trifluoro-1-phenyl-1,3-butanedione in the manner of General Procedure H using molecular sieves 4A as the dehydrating agent over a reaction time of 13 hours to provide the title compound. A portion of the resulting resin (0.05 g) was cleaved with 10% TFA/DCM (0.9 mL) for 2 hours. Resin was filtered off, and the filtrate evaporated under vacuum to afford the 2-(amidomethyl)amino-4-trifluoromethyl-6-phenylpyrimidine. MS $(M+H)^+$ 296.8. ^{1}H-NMR in $CDCl_3$ (δ, ppm): 4.31 (s, 2H, CH_2), 6.28 (br, s, 1H, NH), 6.61 (br, s, 1H, NH), 6.97 (br, s, 1H, NH), 7.45 (s, 1H, CH), 7.50-7.62 (m, 3H, Ar), 8.07 (d, 2H, J=7.4 Hz, Ar).

Example 61 -- Preparation of an 6 Member Library of Soluble Pyrimidine Compounds

FIG. 6 illustrates a synthetic scheme to prepare a library of soluble pyrimidine compounds via a solid support.

Specifically, in FIG. 6, the FMOC protecting group is removed from three different FMOC-NH-RINK resin and then converted to guanadine derivatives 31, 32, and 33 in a manner similar to General Procedure G above. The resulting guanadino compounds are pooled together and then split into two groups. The first group is contacted with

an excess of 4,4,4-trifluoro-1-phenyl-1,3-butanedione in the manner of General Procedure H using molecular sieves 4A as the dehydrating agent to provide for 3 solid phase pyrimidine compounds (not shown). The second group is contacted with an excess of 4,4,4-trifluoro-1-(2-thienyl)-1,3-butanedione in the manner of General Procedure H using molecular sieves as the dehydrating agent to provide for 3 additional solid phse pyrimidine compounds (not shown).

The resin from each of the 6 solid phase pyrimidine compounds prepared above is cleaved with TFA. The resin is filtered off, and the filtrate evaporated under vacuum to afford soluble pyrimidine compounds 34, 35, 36, 37, 38 and 39.

Example 62 -- Solid Phase Synthesis of Pyrido[2,3-d]pyrmidine Compounds

FIG. 8 illustrates that the use of 2-aminouracil in place of an enamino compound leads to the solid phase synthesis of pyrido[2,3-d]pyrimidine compounds. The reaction otherwise proceeds as above and the table below illustrates compounds prepared via this method.

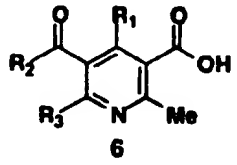
Solid-Phase Synthesis of Pyrido[2,3-d]pyrimidines

Entry #	R_1	R_2	R_3	HPLC product purity, %[a]	MS
1	Ph(^{13}C)	H	H	91	O'K
2	Ph(^{13}C)	Me	Me	93	O'K
3	Ph	Me	Me	99	O'K
4	Ph	Et	Et	98	O'K
1	Ph	H	H	93	O'K
2	Ph	H	All	100	O'K

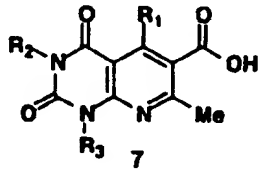
Notes: [a]Detection at 220 nm. [b]Made using synthesizer.

Additionally, FIG. 11 illustrates a more detailed synthesis of substituted nicotinic acids and pyrido[2,3-d]pyrimidines. The synthetic scheme illustrates coupling of the β-ketoester to a polystyrene or Tentagel resin followed by Knoevengal condensation using EDAA or piperidine catalyst in isopropanol/benzene at an elevated temperature. Alternatively, the Knowevengal reaction can employ DMF and TMOF. Subsequent steps are preformed as above.

The table below illustrates pyridine and pyrido[2,3-d]pyrimidine compounds prepared as above.



6



7

Solid Phase Synthesis of Pyridines 6 and Pyrido[2,3-d]pyrimidines 7

Compound #	R_1	R_2	R_3	HPLC purity,[a] %
6a	Ph(^{13}C)[b]	MeO	Me	80 (91[c])
6b	Ph(^{13}C)[b]	i-PrO	Me	95
6c	p-HOOCC$_6$H$_4$	MeO	Me	99
6d	o-FC$_6$H$_4$	MeO	Me	98
6e	2-naphthyl	MeO	Me	98
6f	4-Py	iPrO	Me	81
6g	m-O$_2$NC$_6$H$_4$	MeO	Me	95
6h	p-MeOC$_6$H$_4$	i-PrO	Me	90
6i	n-Hexyl	MeO	Me	90
6j		MeO	Me	70
6k	Ph	MeO	Me	90
6l		MeO	Me	70
6m	Ph	Me	Me	90
6n	Ph	$CH_2CMe_2CH_2$		90
6o	H[d]	Me	Me	80
6p	Ph(^{13}C)[b]	Me	PhCONH	95
7a	Ph(^{13}C)[b]	H	H	91
7b	Ph(^{13}C)[b]	Me	Me	90 (93[c])
7c	Ph	Et	Et	98
7d	Ph	H	All	100

[a]HPLC data for crude products, detection at 220 nm.[10] Essentially quantitative yields for all crude products were observed. [b]Prepared using Ph^{13}CHO. Reaction followed by gel-phase ^{13}C NMR. [c]Yields for products made on Sasrin resin. All other compounds were obtained on Wang resin. [d]Made with i-PrCHO on Wang resin.

Example 63 – Solid Phase Synthesis of 2-Aminopyrimidine Compounds

While several examples of guanylation and the solid phase synthesis of pyrimidines employing relatively non-hindered amino acids, guanylations of α-amino acids with pyrazole-1-carboxamidine hydrochloride (PCA) were not satisfactory in all cases, including phenylalanine and valine, whereas alanine afforded the expected guanidine.

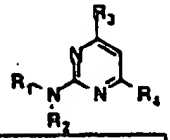
Potentially more reactive benzotriazole-1- and 1,2,3-triazole-1-carboxamidine hydrochlorides (prepared from the respective heterocycles with cyanamide) did not offer significant advantages over the pyrazole reagent PCA (although some increase in guanylation rate of glycine was observed for this reaction with 1,2,3-triazole-1-carboxamidine).

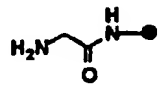
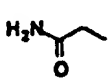
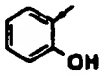
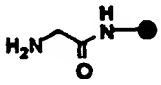
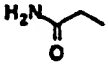
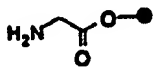
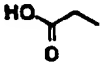
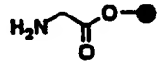
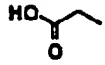
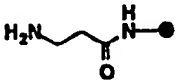
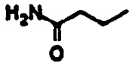
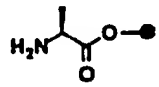
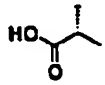
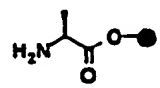
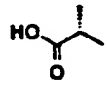
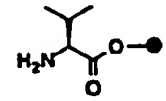
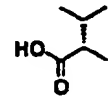
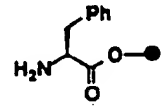
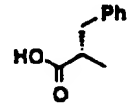
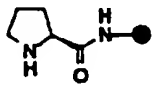
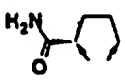
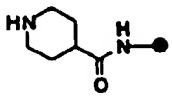
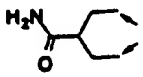
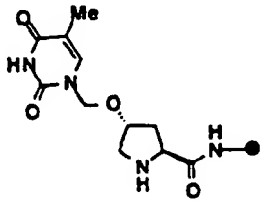
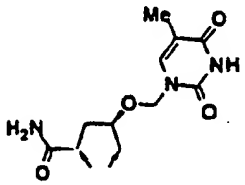
Solid phase guanylation of immobilized amino acids has now been achieved with 1-amidinosulfonic acid $NH{=}C(NH_2)SO_3H$ (ASA).

ASA was readily prepared by oxidation of the commercial amidinosulfinic acid $NH{=}C(NH_2)SO_2H$ with peracetic acid. Typically, this guanylation is performed in methanol at 65-70°C utilizing large excess of the ASA reagent.

FIG. 10 illustrates the solid phase synthesis of pyrimidines prepared using such guanylation reactions. Examples of pyrimidines made according to FIG. 10 are shown in the table below. FIG. 10 illustrates conventional coupling of an FMOC protected amino acid (including natural and unnatural amino acids) to a solid resin through the carboxyl group followed by deprotection with piperidine/DMF. Next, guanalyation is accomplished either with PCA or ASA and then the reaction proceeds as above to provide for the pyrimidine compounds.

Solid Phase Synthesis of 2-Aminopyrimidine Derivatives[a]



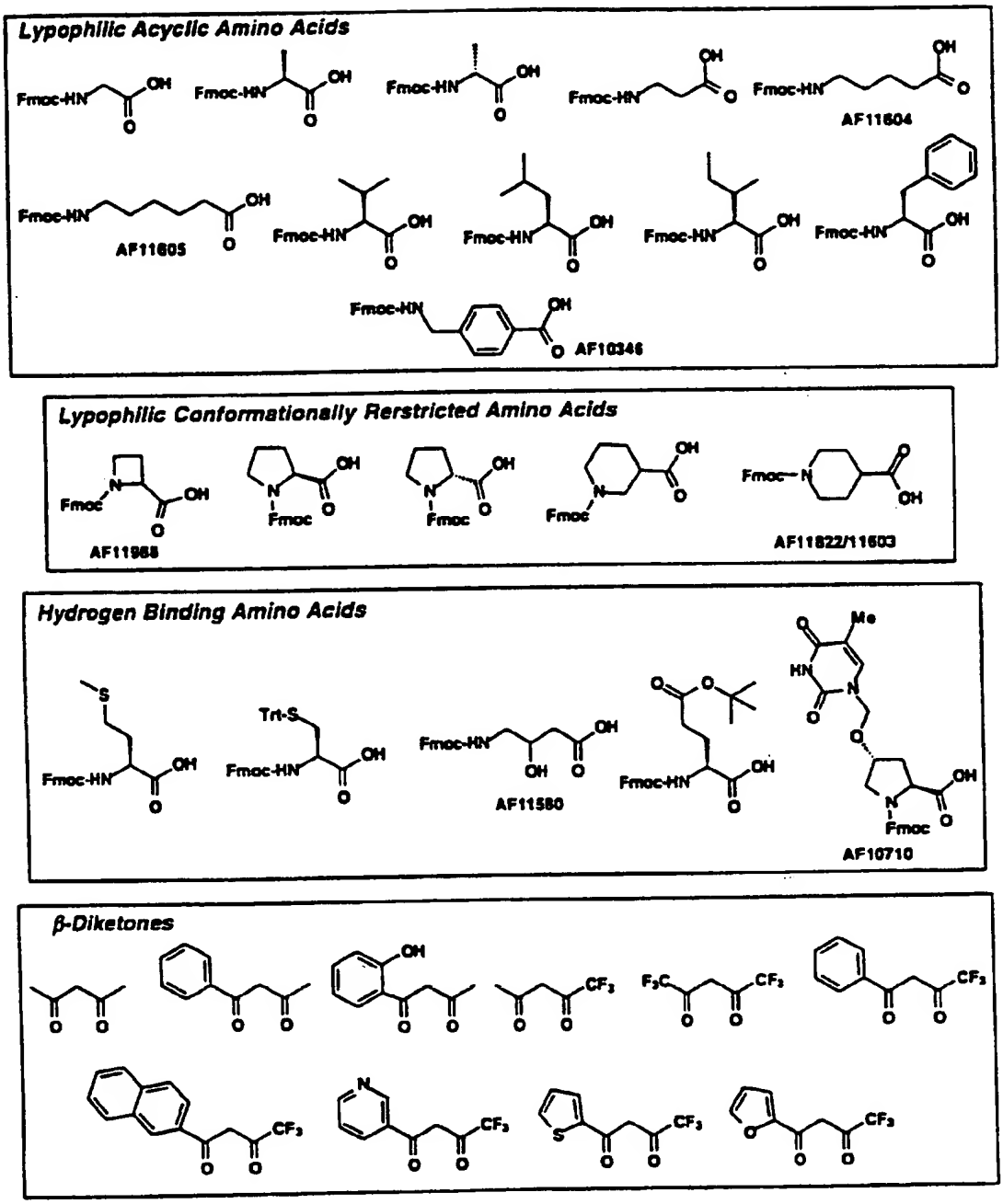
entry #	Starting Amine Resin [b]	derivative				HPLC purity (%) [c]
		R_1	R_2	R_3	R_4	
1			H	Me	Me	>75% [d]
2		H	H	Me		94
3			H	Ph	Ph	75
4			H	CF_3		96
5			H	CF_3		97
6			H	CF_3		95
7			H	CF_3	Ph	74
8			H	CF_3		70
9			H	CF_3		70
10			H	CF_3		60
11				CF_3		80
12				CF_3	Ph	78
13				CF_3		70

Notes: [a]Products were identified by MS and/or NMR spectra. [b]Amides were made on Rink resin, whereas carboxylic acids - using Sasrin support, except for the compound of entry 7 made on Tentagel S PHB resin. Amino acids of entries 1-7 were guanylated with PCA, while ASA was used in all other cases (see Scheme 8). [c]Detection at 220 nm. [d]By ^{1}H NMR. [e]PAL resin.

As seen from the table above, series of natural and unnatural amino acids have been successfully converted into corresponding 2-aminopyrimidine derivatives on a solid support. The method tolerates aromatic/heteroaromatic substitutions in both amino acid substrates and diketone reagents, and introduction of certain groups is now achievable (see, e.g., phenolic derivative of the entry 2 and amino acid nucleoside derivative of the entry 13). Preparation of 2-aminopyrimidine with unsubstituted amine function from PAL-immobilized guanidine was also possible (Table, entry 2). HPLC purity of pyrimidines thus obtained was in a range of 60-97%. Surprisingly, the quality of valine derivative (entry 9) has superseded that of phenylalanine-derived pyrimidine of entry 10 (HPLC purites 70 and 60%, respectively).

Example 64 -- Construction of Combinatorial Library of 2-Aminopyrimidines

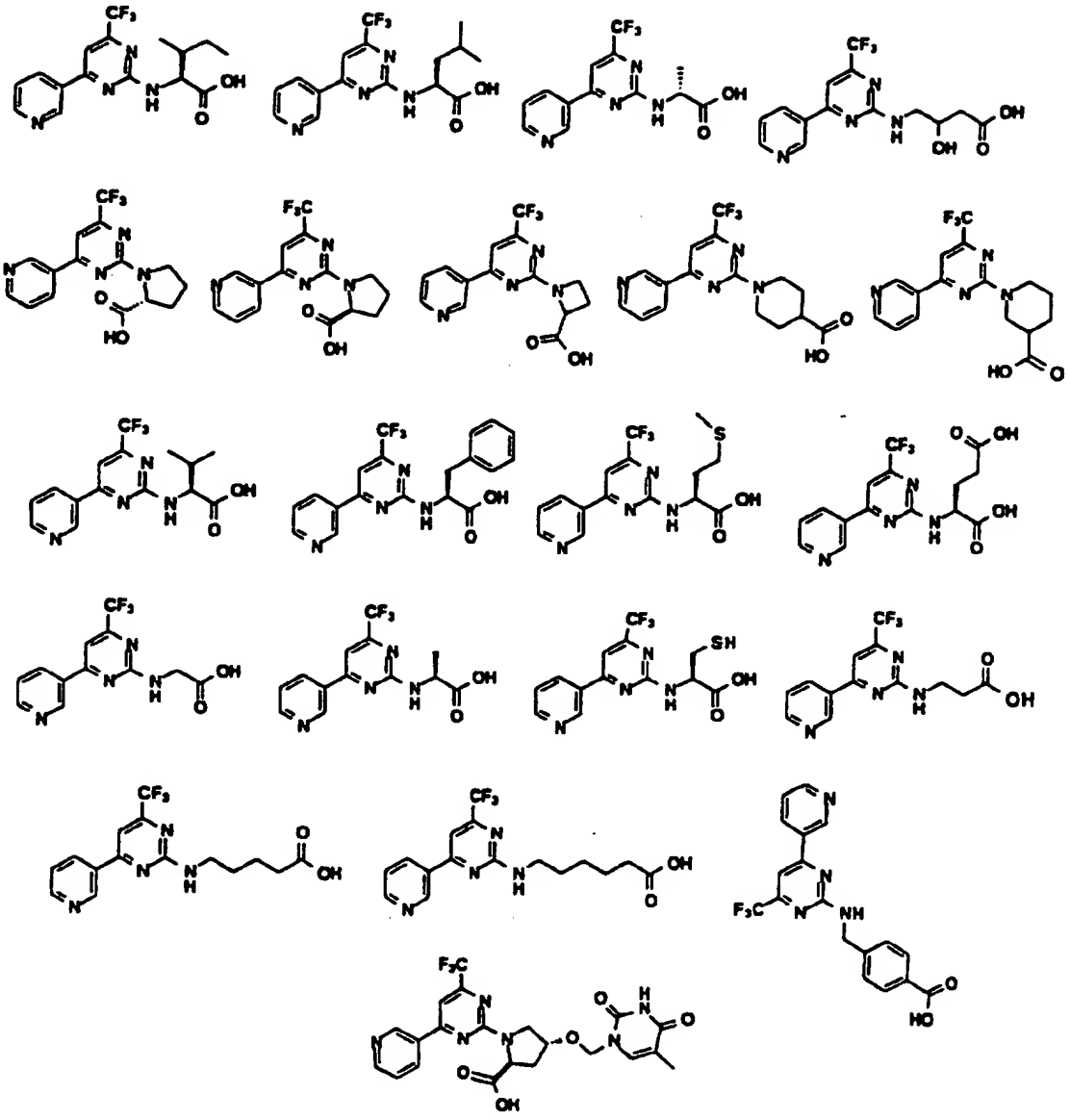
Using the procedures set forth above, a pyrimidine library was synthesized using building blocks listed below.


Lypophilic Acyclic Amino Acids
Fmoc-HN
OH
O
AF11604
AF11605
AF10346
Lypophilic Conformationally Rerstricted Amino Acids
Fmoc
N
AF11988
AF11822/11603
Hydrogen Binding Amino Acids
S
Trt-S
AF11580
Me
HN
AF10710
β-Diketones
CF3
F3C

This library was been designed to incorporate structurally diverse amino acids: (i) lyophilic acyclic amino acids, (ii) lypophilic conformationally restricted amino acids, and (iii) hydrogen binding amino acids. Both commercially available Sasrin-supported building blocks (12 compounds) and in-house made amino acids have been used. The latter were coupled with Sasrin alcohol resin using standard DIC/DMAP protocol. Double coupling has been used to increase the loading of amino acids (typically, loadings of ca. 044-076 mmol/g were achieved; employment of the Mukayama's coupling reagent instead of DIC/DMAP did not provide for significant improvement).

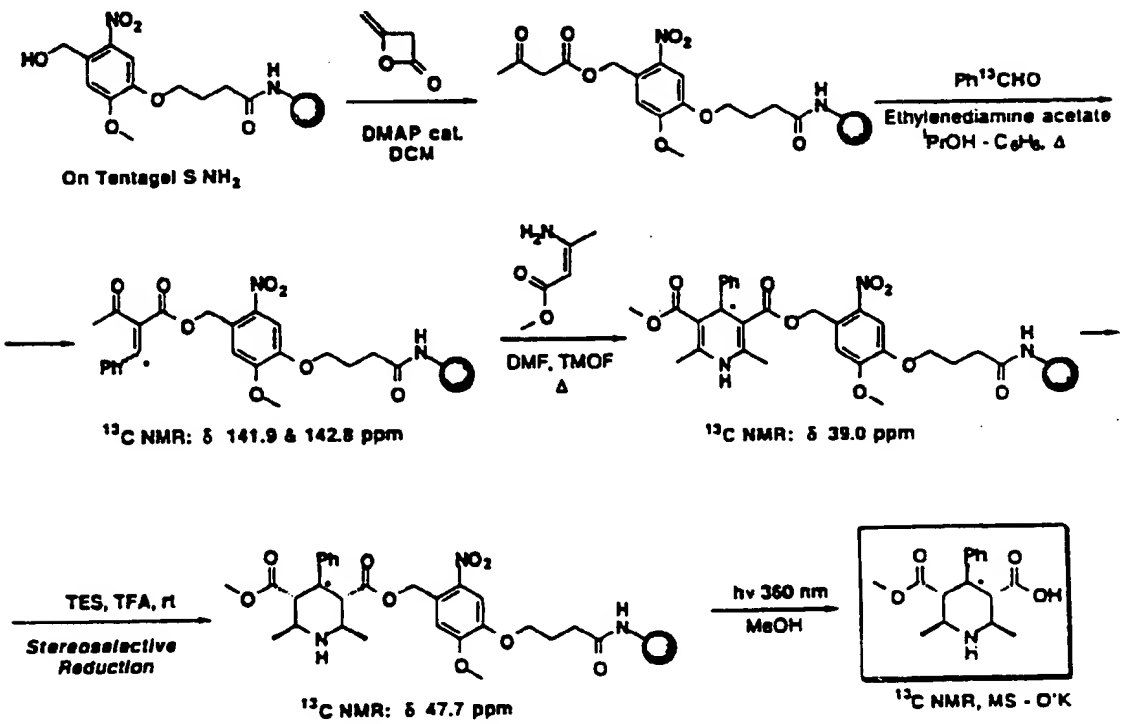
Sasrin-immobilized α-amino acids L-Ala, D-Ala, L-Val, L-Phe, L-Glu(t-Bu), L-Met, L-Cys(Trt) and L-Leu have been guanylated with ASA (see above), whereas PCA was employed in all other cases. Quality of the guanylation was controlled by Kaiser test (negative for resulted guanidine derivatives) and by MS for TFA-cleaved control resin samples. Satisfactory ESI MS were obtained for all 21 (cleaved) guanidines thus obtained.

Next, these tethered intermediates were combined and split into 10 pools. Each of the pools was separately reacted with one of diketone reagents (see above) at 80°C in the presence of molecular sieves 4 A (as dehydrating reagent). Analytical samples of the library ACL0598 were cleaved with 3% triethylsilane and 30% TFA in DCM. Subsequent MS analysis of the pool derived from benzoylacetone indicated the presence of 17 ions from the expected 21 (or 81% of the total number of components). The MS analysis for the pool derived from 4,4,4-trifluoro-1-(3-pyridyl)-1,3-butanedione revealed the presence of all 21 expected pyrimidines (100% of desired components). Structures for the components of the last pool are shown below. Certain impurities have also been detected.



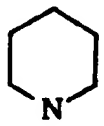
Example 65 – Solid Phase Synthesis of Piperidines

Piperidine compounds are well known as possessing pharmocological activity including activity as cardiovascular agents as set forth in European Patent Application Publication No. 0 158 955 which is incorporated herein by reference in its entirety. The solid phase dihydropyridine compounds described above provide solid phase intermediates for the solid phase synthesis of piperidines. Conversion of the solid phase dihydropyridine compounds to solid phase piperidines is illustrated below:



The reductive reaction stereoselectively provides for an all-*trans* product. Such products can provide for a library to library conversion of dihydropyridine compounds to piperidine compounds.

Preferred piperidine compounds prepared by these methods include those set forth above for the 1,4-dihydropyridine compounds wherein both sites of carbon-carbon unsaturation have been reduced to provide for the piperidine core structure, i.e.,



WHAT IS CLAIMED IS:

1. A library of diverse 1,4-dihydropyridine, 1,4-dihydropyrimidine, pyridine, pyrimidine or piperidine structures comprising a plurality of solid supports having a plurality of covalently bound 1,4-dihydropyridines, 1,4-dihydropyrimidines, pyridines, pyrimidines or piperidines wherein the 1,4-dihydropyridine, 1,4-dihydropyrimidine, pyridine, pyrimidine or piperidine bound to each of the supports is substantially homogeneous and further wherein each compound bound on one support is different from the compounds bound on the other supports.

2. The library according to Claim 1 wherein said plurality of solid supports comprise 1,4-dihydropyridine structures.

3. The library according to Claim 1 wherein said plurality of solid supports comprise 1,4-dihydropyrimidine structures.

4. The library according to Claim 1 wherein said plurality of solid supports comprise pyridine structures.

5. The library according to Claim 1 wherein said plurality of solid supports comprise pyrimidine structures.

6. The library according to Claim 1 wherein said covalently bound 1,4-dihydropyridine, 1,4-dihydropyrimidine, pyridine, pyrimidine or piperidine structures are bound to the solid support via a linking arm.

7. The library according to Claim 6 wherein said linking arm is non-cleavable.

8. The library according to Claim 6 wherein said linking arm is cleavable.

9. The library according to Claim 1 wherein each of said solid supports further comprises a surface bound tag which identifies the molecule attached thereto.

10. A method for preparing a 1,4-dihydropyridine group, a 1,4-dihydropyrimidine group, a pyridine group, a pyrimidine group or a piperidine goupr covalently attached to a solid support which method comprises:

(a) providing for a Knoevenagel condensation product of an aldehyde and a compound selected from a β-keto ester, a β-keto amide and a β-diketone;

(b) contacting this Knoevenagel condensation product with either an enamino compound under conditions effective to provide for the 1,4-dihydropyridine group or with an amidine compound under conditions effective to provide for the 1,4-dihydropyrimidine group; and

(c) optionally oxidizing the 1,4-dihydropyridine or 1,4-dihydropyrimidine group to a pyridine group or a pyrimidine group respectively or optionally reducing the 1,4-dihydropyridine to a piperidine group

wherein the Knoevenagel condensation product or the enamino/amidine compound is covalently attached to a solid support.

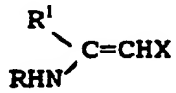
11. The method according to Claim 10 wherein the Knoevenagel condensation product is contacted with an enamino compound to provide for 1,4-dihydropyridine groups.

12. The method according to Claim 10 wherein the Knoevenagel condensation product is contacted with an amidine compound to provide for 1,4-dihydropyrimidine groups.

13. The method according to Claim 10 wherein the Knoevenagel condensation product is formed in the presence of the enamino or amidine compound so that upon condensation, it *in situ* reacts with said enamino or amidine compound to provide for a 1,4-dihydropyridine group or a 1,4-dihydropyrimidine group.

14. The method according to Claim 10 wherein the Knoevenagel condensation product is formed by contacting an alkyl or aromatic aldehyde with a β-keto ester or amide compound where optionally the keto group is masked under conditions which effect condensation.

15. The method according to Claim 11 wherein the enamino compound is represented by the formula:



where R is selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms;

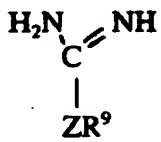
R^1 is selected from the group consisting of hydrogen, alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and 1 to 5 halo atoms, thioalkyl of from 1 to 6 carbon atoms, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, aryl of from 6 to 10 carbon atoms optionally substituted with from 1 to 2 substituents selected from the group consisting of nitro, cyano, halo, alkyl of from 1 to 6 carbon atom, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo substituents, and $-NR^3R^4$ where

R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms; and

X is selected from the group consisting of $-C(O)R^2$, $-S(O)_2R^2$, cyano, nitro and $-PO(OR^2)_2$ where R^2 is alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkoxy of from 1 to 6 carbon atoms, alkalkoxy of from 2 to 8 carbon atoms and from 1 to 3 ether oxygens, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, alkamino of from 2 to 6 carbon atoms, N-alkylalkamino of from 2 to 10 carbon atoms and N,N-dialkylalkamino of from 3 to 12 carbon atoms

wherein, optionally, the enamino compound is covalently attached to a compatible solid support via the R, R^1 or X substituent.

16. The method according to Claim 12 wherein said amidine compound is represented by the formula:



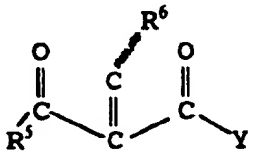
wherein R^9 is selected from the group consisting of hydrogen, alkyl of from 1 to 6 carbon atoms optionally substituted with from 1 to 5 substituents selected from the group consisting of halogen, hydroxyl, nitro, cyano, alkoxy of from 1 to 6 carbon atoms, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, carboxyl, and $-C(O)NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, aryl of from 6 to 10 carbon atoms optionally substituted with from 1 to 3 substituents selected from halogen, hydroxy, nitro, cyano, alkyl of from 1 to 6 carbon atoms and alkoxy of from 1 to 6 carbon atoms, alkaryl of from 7 to 12 carbon atoms optionally substituted

with from 1 to 3 substituents on the aryl ring which substituents are selected from halogen, hydroxy, nitro, cyano, alkyl of from 1 to 6 carbon atoms and alkoxy of from 1 to 6 carbon atoms, heterocyclic of from 2 to 5 carbon atoms and from 1 to 3 hetereoatoms selected from oxygen, nitrogen and sulfur, and an amino acid residue; and

Z is selected from the group consisting of O, NH and S and

where optionally, the amidine compound is covalently linked to a compatible solid support via the imidazole ring or the Z substituent.

17. The method according to Claim 10 wherein the Knoevenagel condensation product is represented by the formula:



wherein

R^5 is hydrogen, a linear alkyl group of from 1 to 6 carbon atoms or an aryl group of from 6 to 10 carbon atoms,

R^6 is alkyl of from 1 to 6 carbon atoms, aryl of from 6 to 10 carbon atoms optionally substituted with from 1 to 2 substituents selected from the group consisting of nitro, cyano, halo, alkyl of from 1 to 6 carbon atom, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkoxy of from 1 to 6 carbon atoms, carboxyl and $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, or a heterocyclic group of from 2 to 9 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, and

Y is selected from the group consisting of alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo atoms, alkoxy of from 1 to 6 carbon atoms, alkalkoxy of from 2 to 8

carbon atoms and from 1 to 3 ether oxygens, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms and optionally Y and R^5 are joined to form a cyclic or heterocylic structure fused to the 1,4-dihydropyridine ring which structure contains from 2 to 6 carbon atoms and optionally from 1 to 3 hetero atoms selected from oxygen, nitrogen and sulfur

still further wherein, optionally, the condensation product is covalently attached to a compatible solid support via the Y or R^6 substituent.

18. The method according to Claim 11 wherein the 1,4-dihydropyridine group is oxidized to the pyridine group.

19. The method according to Claim 12 wherein the 1,4-dihydropyrimidine group is oxidized to the pyrimidine group.

20. A method for preparing a synthetic 1,4-dihydropyridine, a synthetic 1,4-dihydropyrimidine, a synthetic pyridine or a synthetic pyrimidine compound library produced by synthesizing on each of a plurality of solid supports a single compound wherein each compound comprises a 1,4-dihydropyridine group, a 1,4-dihydropyrimidine group, a pyridine group or a pyrimidine group which library is synthesized in a process comprising:

a) apportioning the supports comprising a covalently bound Knoevenagel condensation product or a covalently bound compound selected from the group consisting of an enamino group or an amidine group among a plurality of reaction vessels, and

b) exposing the supports in each reaction vessel under conditions wherein the condensation product or the enamino group is converted to a 1,4-dihydropyridine group or wherein the condensation product or the

amidine group is converted to a 1,4-dihydropyrimidine group provided that at least one of the following conditions is satisfied:

1) at least two different Knoevenagel condensation products are used to produce the 1,4-dihydropyridine or 1,4-dihydropyrimidine groups;

2) at least two different enamino or amidine groups are used to produce the 1,4-dihydropyridine or 1,4-dihydropyrimidine groups; and

3) at least two different sets of reaction conditions are used to produce the 1,4-dihydropyridine or the 1,4-dihydropyrimidine groups; and

c) optionally oxidizing the 1,4-dihydropyridine or the 1,4-dihydropyrimidine group to a pyridine group or a pyrimidine group respectively.

21. The method according to Claim 20 wherein a Knoevenagel condensation product and an enamino compound are contacted with each other to provide for a 1,4-dihydropyridine group.

22. The method according to Claim 20 wherein a Knoevenagel condensation product and an amidine compound are contacted with each other to provide for 1,4-dihydropyrimidine groups.

23. The method according to Claim 20 wherein each reaction vessel contains a different compound.

24. The method according to Claim 20 which further comprises pooling the supports.

25. The method according to Claim 20 wherein said Knoevenagel condensation product or said enamino/amidine group is covalently bound to the solid support via a linking arm.

26. The method according to Claim 25 wherein said linking arm is non-cleavable.

27. The method according to Claim 25 wherein said linking arm is cleavable.

28. The method according to Claim 20 wherein said solid support further comprises a surface bound tag which identifies the molecule attached thereto.

29. The method according to Claim 21 wherein said 1,4-dihydropyridine group is oxidized to a pyridine group.

30. The method according to Claim 22 wherein said 1,4-dihydropyrimidine group is oxidized to a pyrimidine group.

31. The method according to Claim 21 wherein each of said supports contains a compound having a different 1,4-dihydropyridine group.

32. The method according to Claim 22 wherein each of said supports contains a compound having a different 1,4-dihydropyrimidine group.

33. The method according to Claim 29 wherein each of said supports contains a compound having a different pyridine group.

34. The method according to Claim 30 wherein each of said supports contains a compound having a different pyrimidine group.

35. The method according to Claim 20 wherein said supports comprise a Knoevenagel condensation product covalently bound thereto which is converted to a 1,4-dihydropyridine group by reaction with a soluble enamino compound or is converted to a 1,4-dihydropyrimidine group by reaction with a soluble amidine compound.

36. The method according to Claim 25 wherein the Knoevenagel condensation product covalently bound to the solid support is formed in the presence of the enamino or amidine compound so that upon condensation, it *in situ* reacts with said enamino compound to provide for a 1,4-dihydropyridine group or with the amidine compound to provide for a 1,4-dihydropyrimidine.

37. The method according to Claim 20 wherein said supports comprise an enamino group or an amidine group covalently bound thereto which, when an enamino group is present, is converted to a 1,4-dihydropyridine group by reaction with a Knoevenagel condensation product or, when an amidine group is present, is converted to a 1,4-dihydropyrimine group by reaction with a Knoevenagel condensation product.

38. A method for preparing a synthetic 1,4-dihydropyridine, a synthetic 1,4-dihydropyrimidine, a synthetic pyridine or a synthetic pyrimidine compound library which library is synthesized in a process comprising:

a) apportioning supports comprising a linking arm having a reactive amino or hydroxyl functionality into a plurality of reaction vessels,

b) combining into each reaction vessel a different β-keto ester, β-keto amide or β-diketone or a different β-keto ester, β-keto amide or

β-diketone precursor such that the β-keto ester, β-keto amide or β-diketone becomes covalently attached to the linking arm of the supports through the amino or hydroxyl functionality wherein, in the case of the β-keto ester, β-keto amide or β-diketone precursors, the attachment converts these precursor groups to a β-keto ester β-keto amide or β-diketone group respectively,

c) pooling the supports and then apportioning the supports among a plurality of reaction vessels,

d) combining into each reaction vessel a different aldehyde under conditions wherein the β-keto ester, the β-keto amide or the β-diketone forms a Knoevenagel condensation product with the aldehyde,

e) pooling the supports produced in d) above and then apportioning the supports among a plurality of reaction vessels,

f) combining into each reaction vessel a different enamino group or a different amidine group under conditions wherein the Knoevenagel condensation product and the enamino or amidine group form an adduct,

g) cyclizing the adduct to form a 1,4-dihydropyridine compound when an enamino group is employed and a 1,4-dihydropyrimidine compound when an amidine group is employed, and

h) optionally oxidizing the 1,4-dihydropyridine or the 1,4-dihydropyrimidine group to a pyridine or pyrimidine group respectively.

39. The method according to Claim 38 wherein the Knoevenagel condensation product is contacted with an enamino compound to provide for a 1,4-dihydropyridine group.

40. The method according to Claim 38 wherein the Knoevenagel condensation product is contacted with an amidine compound to provide for 1,4-dihydropyrimidine groups.

41. The method according to Claim 38 wherein, prior to procedure g), the adduct is separated from the support and then converted to either the 1,4-dihydropyridine or 1,4-dihydropyrimidine compound.

42. The method according to Claim 38 wherein, after procedure g), the 1,4-dihydropyridine or 1,4-dihydropyrimidine compound is separated from the support.

43. The method according to Claim 39 wherein said 1,4-dihydropyridine group is oxidized to a pyridine group.

44. The method according to Claim 40 wherein said 1,4-dihydropyrimidine group is oxidized to a pyrimidine group.

45. A method for preparing a synthetic 1,4-dihydropyridine, a synthetic 1,4-dihydropyrimidine, a synthetic pyridine or a synthetic pyrimidine compound library which library is synthesized in a process comprising:

(a) apportioning supports comprising a linking arm having a reactive amino or hydroxyl functionality into a plurality of reaction vessels,

(b) combining into each reaction vessel a different enamino/amidine group or a different enamino/amidine precursor group such that the enamino/amidine group or the enamino/amidine precursor group becomes covalently attached to the linking arm through the amino or hydroxyl functionality wherein, in the case of the enamino/amidine precursor groups, the attachment converts the enamino/amidine precursor group to an enamino group or amidine group,

(c) pooling the supports and then apportioning the supports among a plurality of reaction vessels,

(e) combining into each reaction vessel a different Knoevenagel condensation product under conditions wherein the Knoevenagel condensation product and the enamino/amidine group form an adduct,

(f) cyclizing the adduct to form a 1,4-dihydropyridine compound when an enamino group is employed or a 1,4-dihydropyrimidine compound when an amidine group is employed, and

(g) optionally oxidizing the 1,4-dihydropyridine compound or the 1,4-dihydropyrimidine compound to a pyridine compound or a pyrimidine compound respectively.

46. The method according to Claim 45 wherein an enamino compound is employed to provide for a 1,4-dihydropyridine group.

47. The method according to Claim 45 wherein an amidine compound is employed to provide for a 1,4-dihydropyrimidine group.

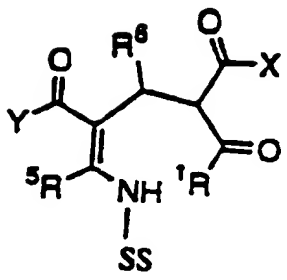
48. The method according to Claim 45 wherein, prior to procedure e), the adduct is separated from the support and then converted to the 1,4-dihydropyridine or the 1,4-dihydropyrimidine compound.

49. The method according to Claim 45 wherein, after procedure e), the 1,4-dihydropyridine or 1,4-dihydropyrimidine compound is separated from the support.

50. The method according to Claim 46 wherein said 1,4-dihydropyridine group is oxidized to a pyridine group.

51. The method according to Claim 47 wherein said 1,4-dihydropyrimidine group is oxidized to a pyrimidine group.

52. A library of diverse solid phase adducts of the formula



wherein:

R^1 is selected from the group consisting of hydrogen, alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and 1 to 5 halo groups, aryl of from 6 to 10 carbon atoms optionally substituted with from 1 to 2 substituents selected from the group consisting of nitro, halo, alkyl of from 1 to 6 carbon atom, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo substituents, and $-NH_2$;

R^5 is hydrogen, a linear alkyl group of from 1 to 6 carbon atoms or an aryl group of from 6 to 10 carbon atoms,

R^6 is alkyl of from 1 to 6 carbon atoms, aryl of from 6 to 10 carbon atoms optionally substituted with from 1 to 2 substituents selected from the group consisting of nitro, halo, alkyl of from 1 to 6 carbon atom, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo substituents, alkoxy of from 1 to 6 carbon atoms, amino, and carboxyl, or a heterocyclic group of from 2 to 9 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, and

X is selected from the group consisting of $-C(O)R^2$, $-S(O)_2R^2$, cyano, nitro and $-PO(OR^2)_2$ where R^2 is alkyl of from 1 to 6 carbon atoms, halo alkyl of from 1 to 2 carbon atoms and from 1 to 5 halo groups, alkoxy of from 1 to 6 carbon atoms, alkalkoxy of from 2 to 8 carbon atoms and from 1 to 3 ether oxygens, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms, alkamino of from 2 to 6 carbon atoms, N-alkyl alkamino of from 2 to 10 carbon atoms and N,N-dialkyl alkamino of from 3 to 12 carbon atoms;

Y is selected from the group consisting of alkyl of from 1 to 6 carbon atoms, haloalkyl of from 1 to 2 carbon atoms and from 1 to 5 halo groups, alkoxy of from 1 to 6 carbon atoms, $-NR^3R^4$ where R^3 and R^4 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 6 carbon atoms and optionally Y and R^5 are joined to form a heterocylic structure fused to the 1,4-dihydropyridine ring which structure contains from 2 to 5 carbon atoms and from 1 to 3 hetereo atoms selected from oxygen, nitrogen and sulfur; and

SS is a solid support.

53. A method for preparing pyrimidine groups covalently attached to a solid support which are prepared by contacting a dicarbonyl compound selected from the group consisting of β-keto ester, a β-keto amide or a β-diketone with an amidine compound under conditions effective to provide for the pyrimidine group wherein the dicarbonyl compound or the amidine compound is covalently attached to a solid support.

54. The method according to Claim 11 wherein the dihydropyridine groups are reduced to piperidine groups.

55. The method according to Claim 21 wherein the dihydropyridine groups are reduced to piperidine groups.

56. The method according to Claim 39 wherein the dihydropyridine groups are reduced to piperidine groups.

57. The method according to Claim 46 wherein the dihydropyridine groups are reduced to piperidine groups.

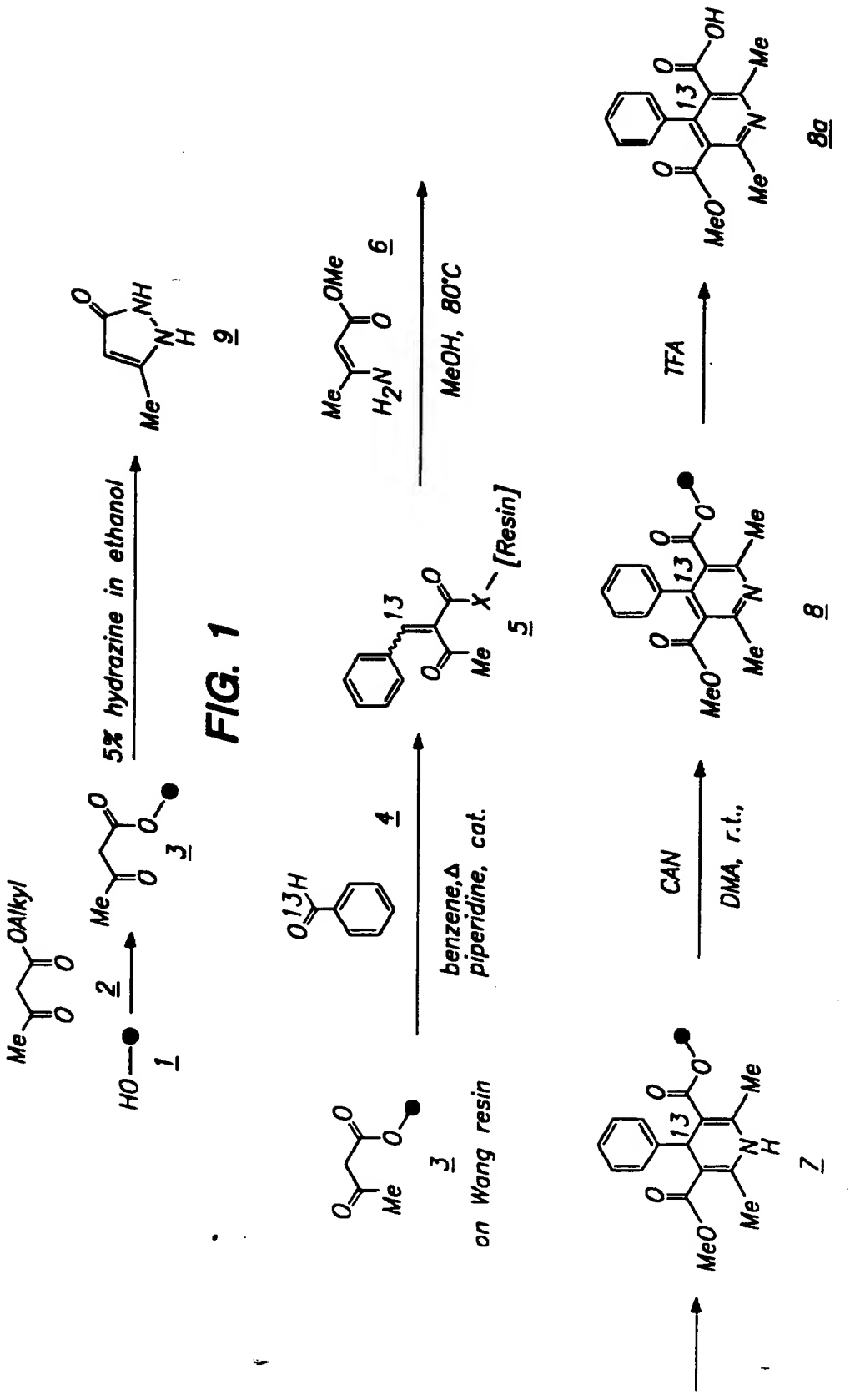


FIG. 1

CAN = ceric ammonium nitrate; DMA = N,N-dimethylacetamide

FIG. 2

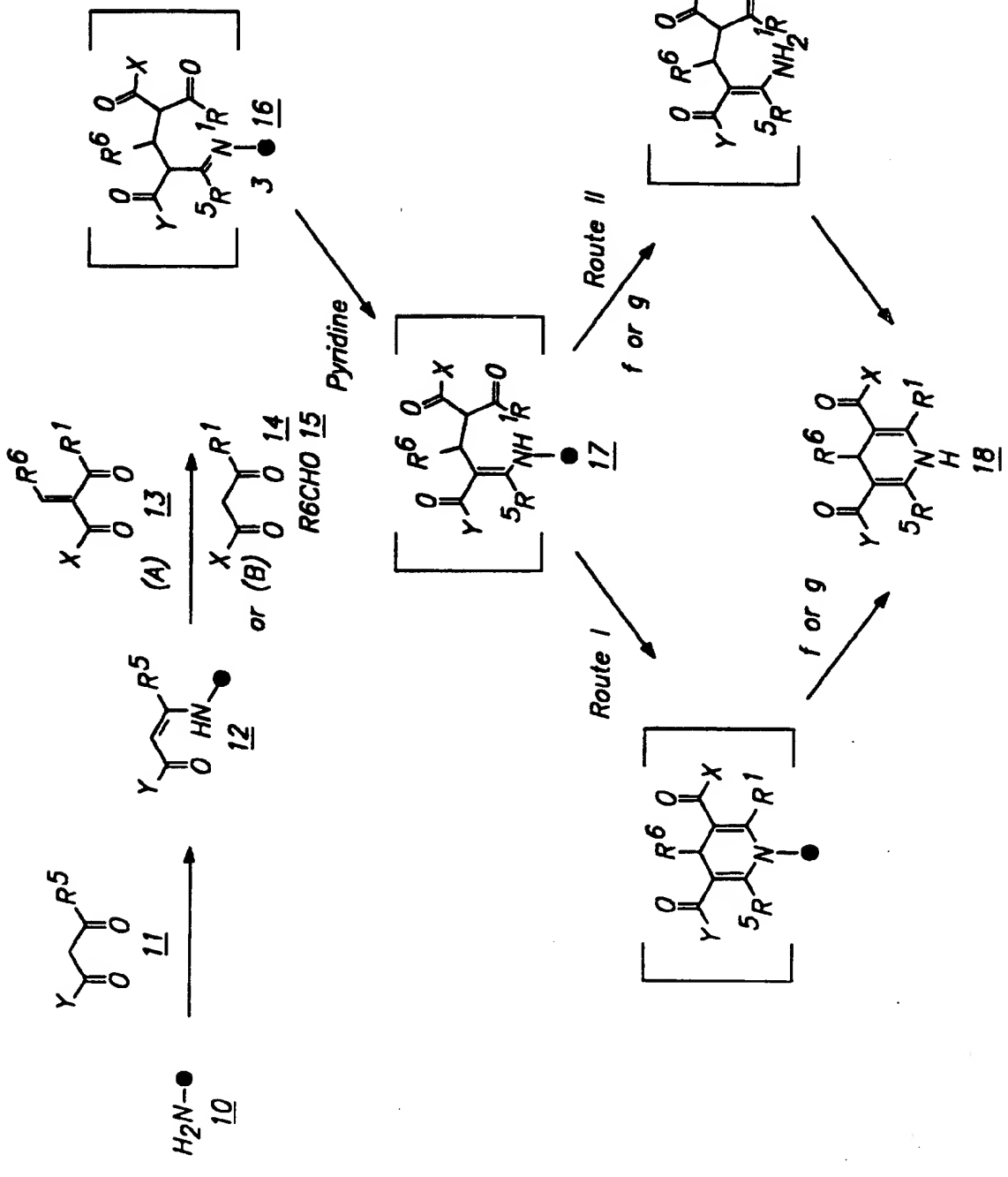

H2N-
10
11
12
(A) 13
or (B) 14
R6CHO 15
3
16
Pyridine
17
Route I
Route II
f or g
f or g
18

FIG. 3

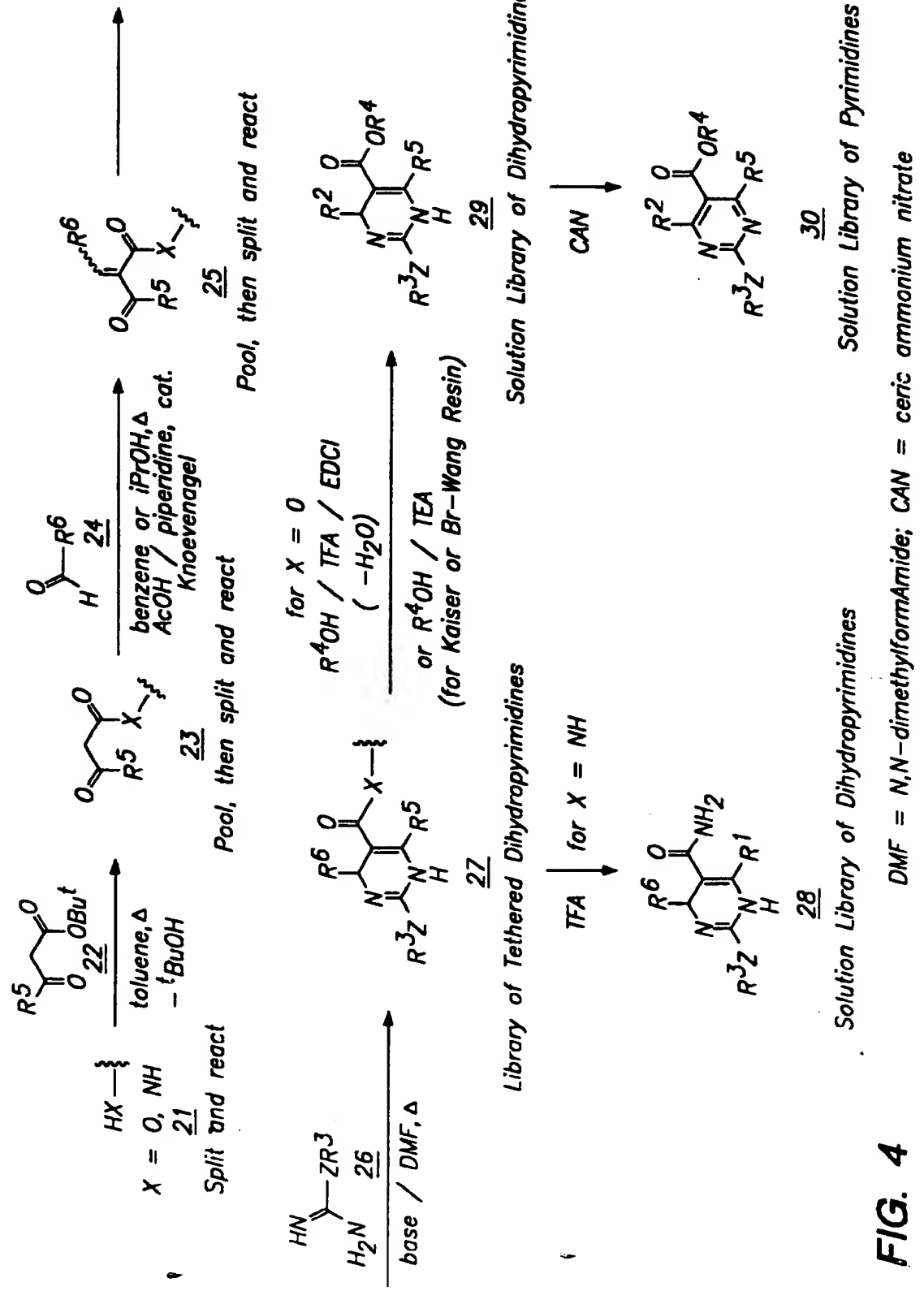
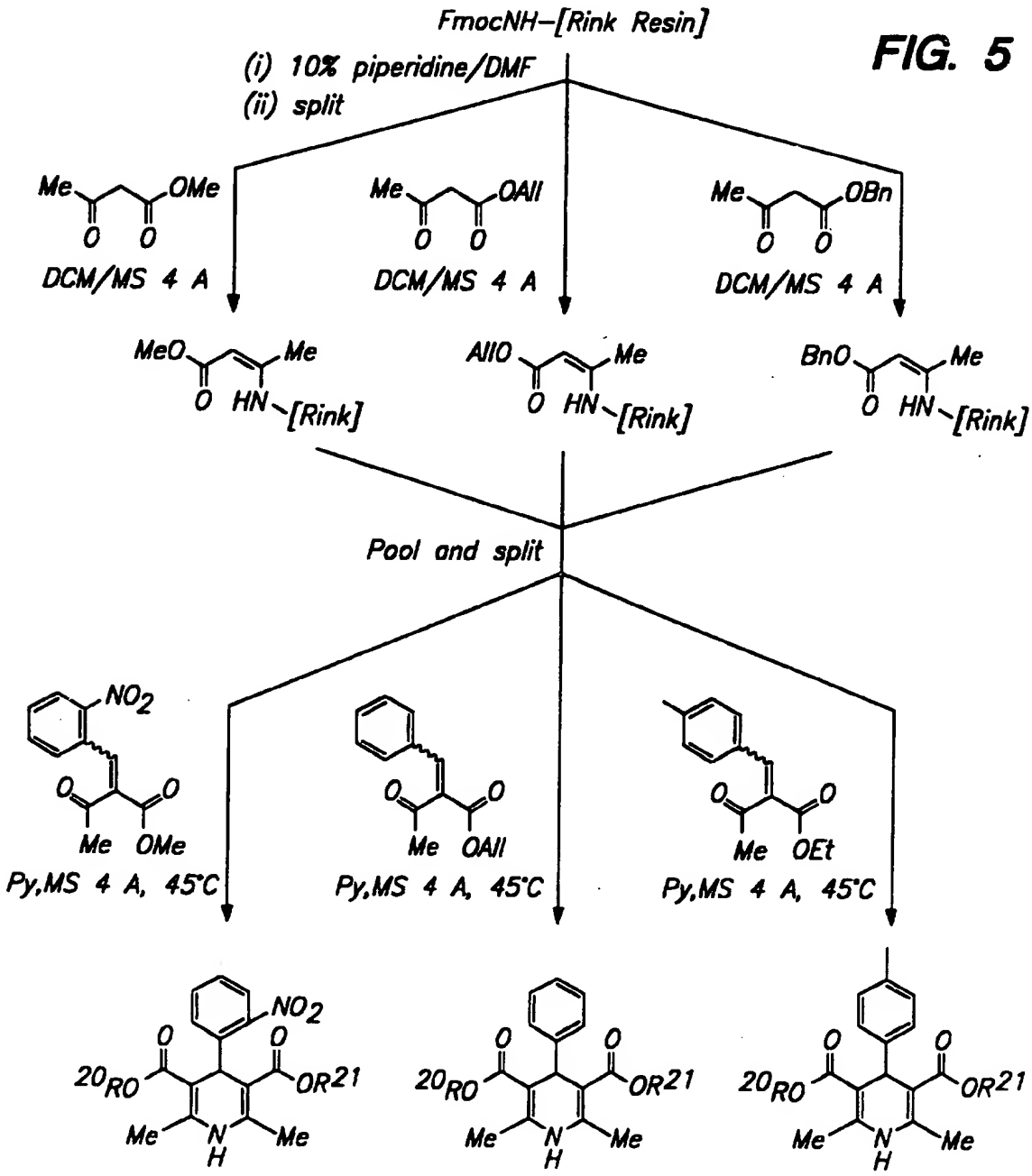

HX—
X = O, NH
21
Split and react
toluene, Δ
– tBuOH
22
Pool, then split and react
benzene or iPrOH, Δ
AcOH / piperidine, cat.
Knoevenagel
24
Pool, then split and react
base / DMF, Δ
26
Library of Tethered Dihydropyrimidines
for X = O
R4OH / TFA / EDCI
(–H2O)
or R4OH / TEA
(for Kaiser or Br–Wang Resin)
Solution Library of Dihydropyrimidines
TFA
for X = NH
Solution Library of Dihydropyrimidines
CAN
Solution Library of Pyrimidines
DMF = N,N–dimethylformAmide; CAN = ceric ammonium nitrate

FIG. 4

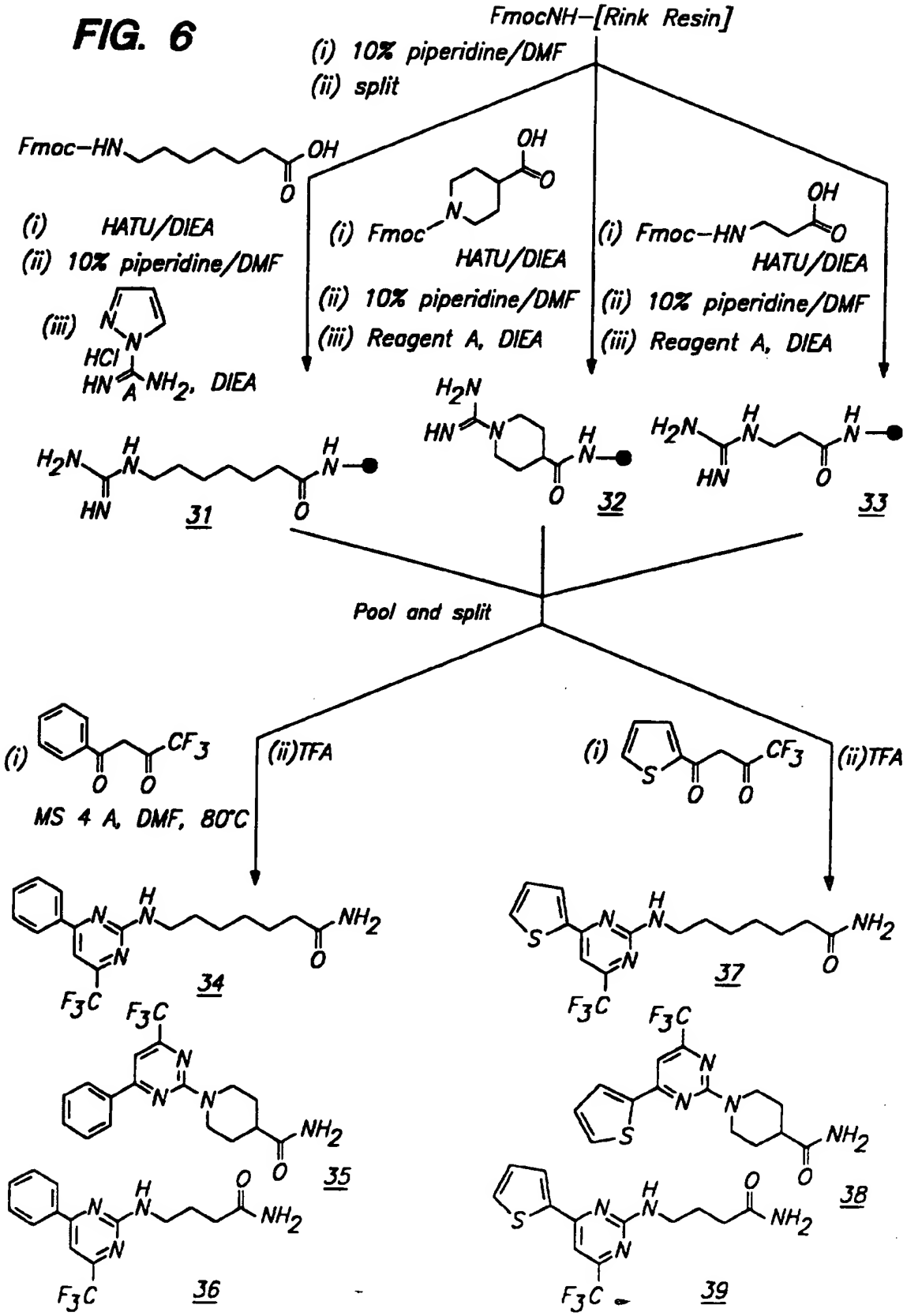
FIG. 5



Subset A	Subset B	Subset C
(1) $R^{20} = R^{21} =$ Me Nifedipine	(4) $R^{20} =$ Me, $R^{21} =$ All	(7) $R^{20} =$ Me, $R^{21} =$ Et
(2) $R^{20} =$ All, $R^{21} =$ Me	(5) $R^{20} = R^{21} =$ All	(8) $R^{20} =$ All, $R^{21} =$ Et
(3) $R^{20} =$ Bn, $R^{21} =$ Me	(6) $R^{20} =$ Bn, $R^{21} =$ All	(9) $R^{20} =$ Bn, $R^{21} =$ Et

DMF = N,N–dimethylformamide; DCM = dichloromethane; Py = Pyridine; MS = molecular sieves; Me = methyl; All = allyl; Bn = benzyl

FIG. 6


FmocNH–[Rink Resin]
(i) 10% piperidine/DMF
(ii) split
Fmoc–HN
OH
O
(i) HATU/DIEA
(ii) 10% piperidine/DMF
(iii)
HCl
HN
A
NH2, DIEA
(i) Fmoc
HATU/DIEA
(ii) 10% piperidine/DMF
(iii) Reagent A, DIEA
(i) Fmoc–HN
HATU/DIEA
(ii) 10% piperidine/DMF
(iii) Reagent A, DIEA
H2N
HN
H
N
31
32
33
Pool and split
(i)
CF3
(ii)TFA
MS 4 A, DMF, 80°C
S
34
35
36
37
38
39
F3C
NH2

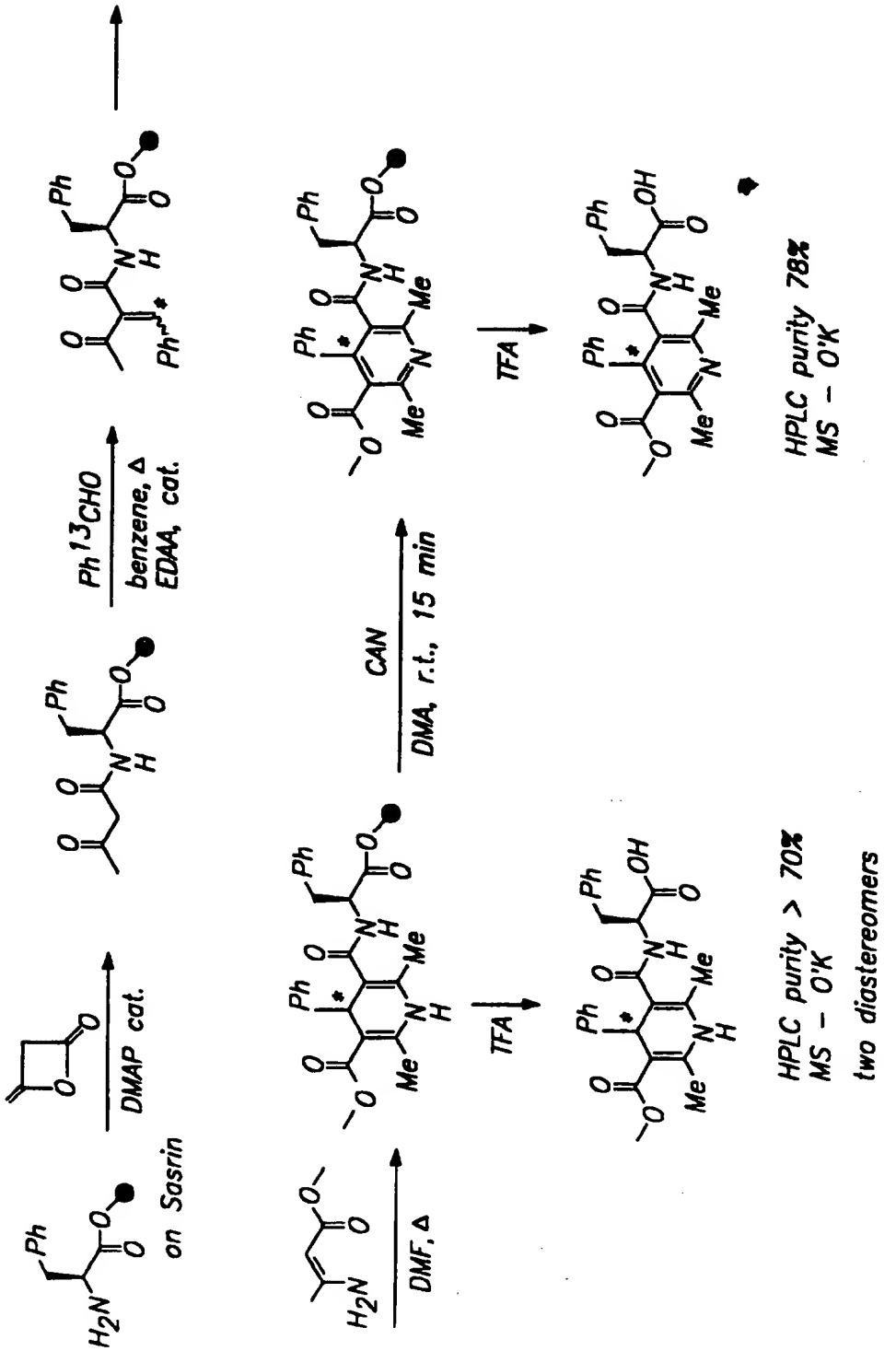

DMAP cat.
on Sasrin
DMF, Δ
TFA
CAN
DMA, r.t., 15 min
TFA
Ph13CHO
benzene, Δ
EDAA, cat.
HPLC purity > 70%
MS – O'K
two diastereomers
HPLC purity 78%
MS – O'K

FIG. 7

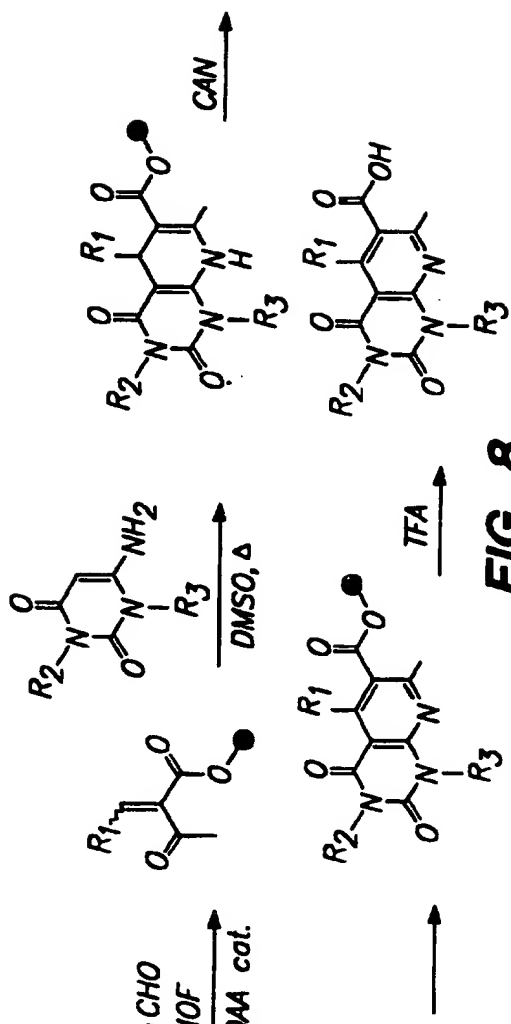

on Wang resin
R1CHO
TMOF
EDAA cat.
DMSO, Δ
TFA
CAN

FIG. 8

Wang resin
HO
(i) Ac2O
DMAP
(ii) LDA
(iii)
13MeCOCl
DMAP
LDA
THF, -78°C
13C NMR: δ 19.9 ppm
13C NMR: δ ca. 45 ppm
(enol form at 83-87 ppm)
R
Conversion
(by13C NMR)
Ph
> 95%
N2H4
EtOH
ca. 40%
Cl

FIG. 9

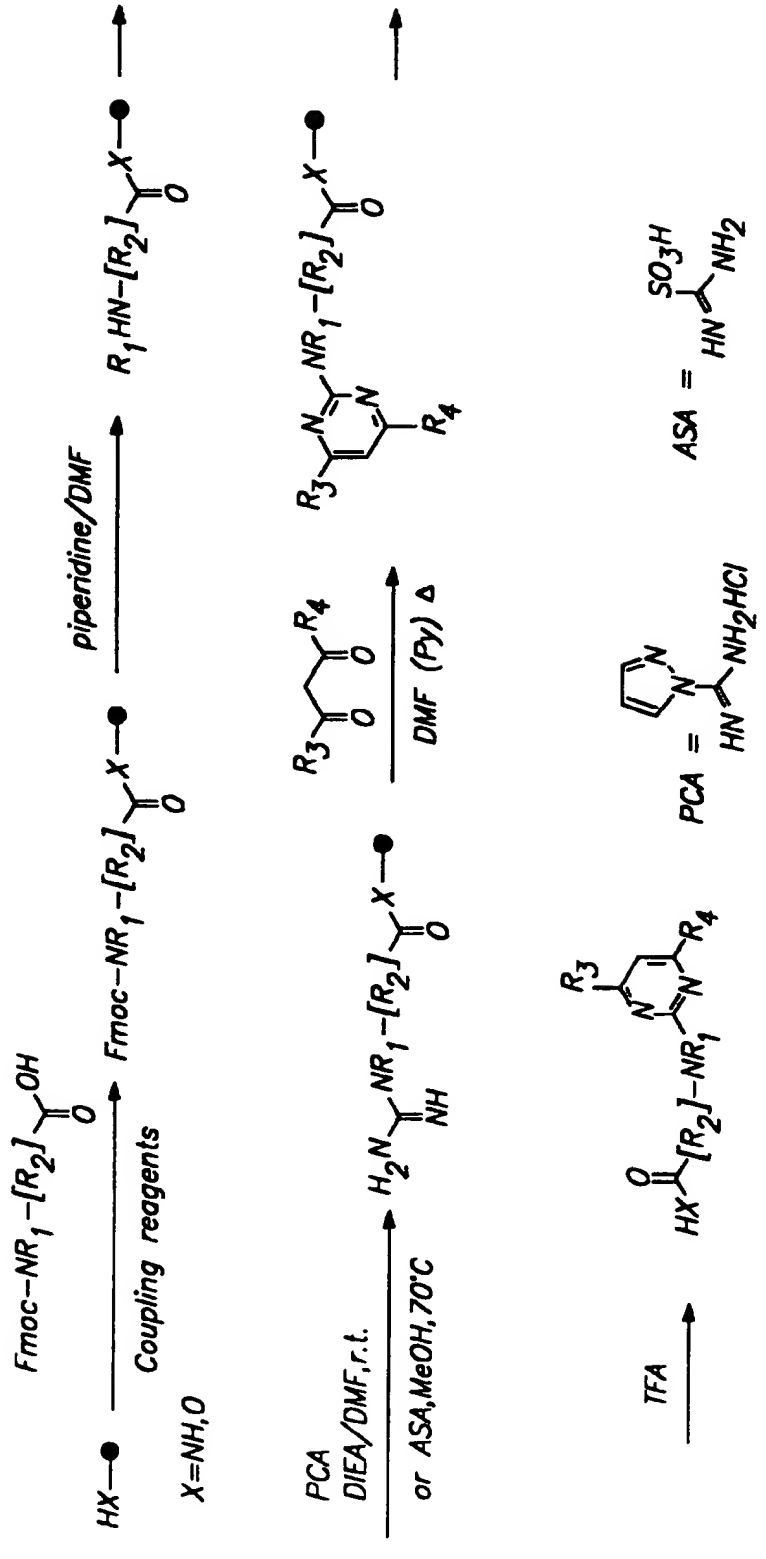

Fmoc–NR1–[R2]–OH
HX
Coupling reagents
X=NH,O
Fmoc–NR1–[R2]–X
piperidine/DMF
R1HN–[R2]–X
PCA
DIEA/DMF,r.t.
or ASA,MeOH,70°C
H2N–NR1–[R2]–X
DMF (Py) Δ
TFA
HX–[R2]–NR1
X=NH,O
PCA =
ASA =

FIG. 10

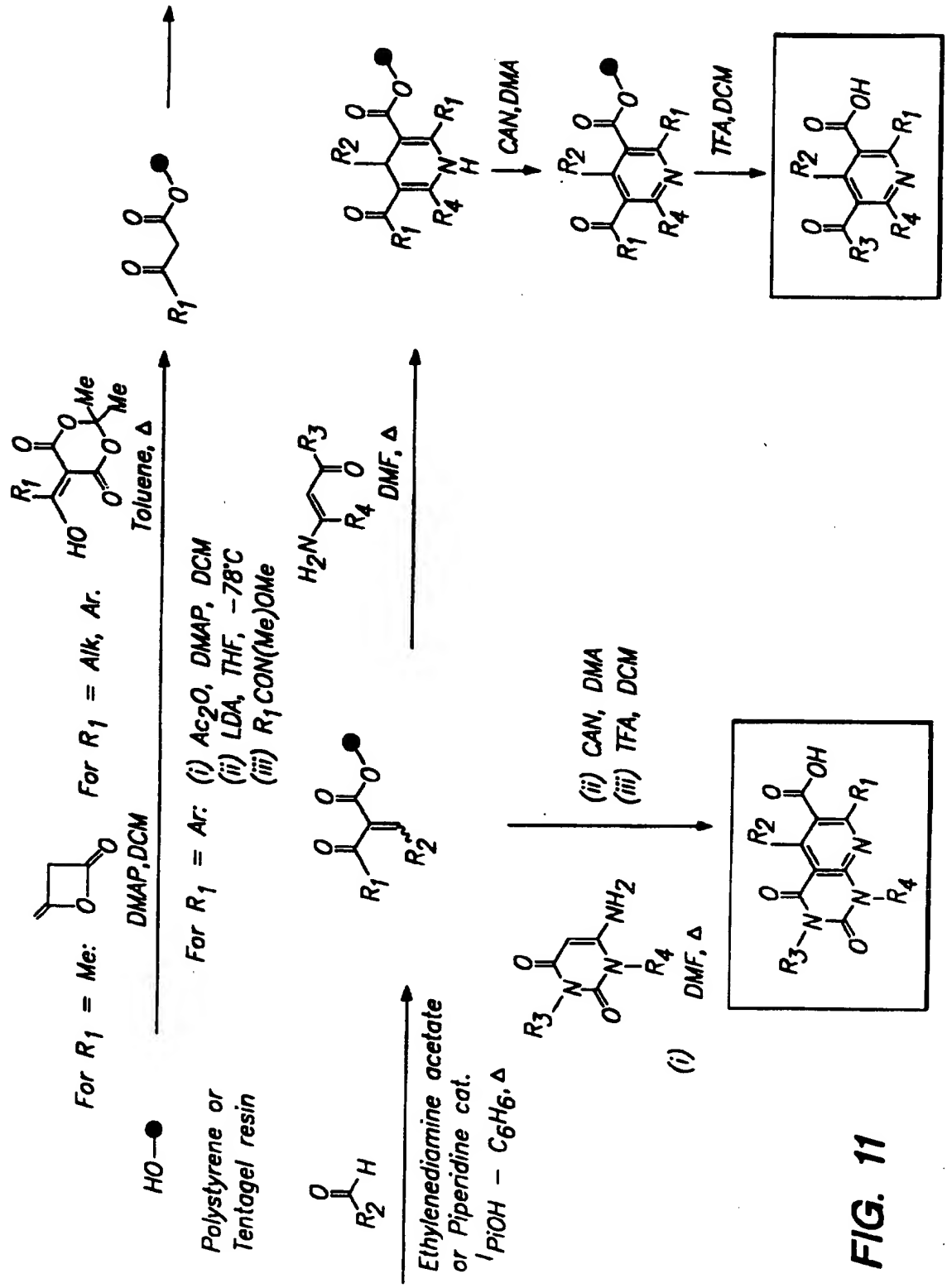

HO—●
Polystyrene or Tentogel resin
For R_1 = Me:
For R_1 = Alk, Ar.
DMAP,DCM
Toluene, Δ
For R_1 = Ar: (i) Ac_2O, DMAP, DCM
(ii) LDA, THF, −78°C
(iii) $R_1CON(Me)OMe$
DMF, Δ
Ethylenediamine acetate or Piperidine cat.
^iPiOH – C_6H_6, Δ
(i) DMF, Δ
(ii) CAN, DMA
(iii) TFA, DCM
CAN,DMA
TFA,DCM

FIG. 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/05956

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 211/02, 221/00, 233/00; C12Q 1/00

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/7.1; 436/518, 523, 527, 528; 523/213; 525/326.7 327.1, 375; 544/246; 546/1, 184

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN Reaction Cluster of Databases

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHO et al. Synthesis of Novel 2-Chloro-1,4-dihydropyridines by Chlorination of 2-Hydroxy-1,4-dihydrophridines with Phosphorus Oxychloride. Chem. Pharm. Bull. August 1989, Vol 37, No.8, pages 2117-2121, especially page 2118.	10, 11, 15, 17
Y	TROSCHULTZ et al. Synthese von 4-Aryl-1,4-dihydro-und 4-Aryl-4,5-dihydro-5-nitro-nicotinsauremethylestern. Arch. Pharm. (Weinheim, Ger.). 1991, Vol 324, No.2, pages 73-77.	10, 11, 15, 17

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 14 AUGUST 1996	Date of mailing of the international search report 18 SEP 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Lyman Smith Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/05956

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ATWAL et al. Dihydropyrimidine Calcium Channel Blockers: 2-Heterosubstituted 4-Aryl-1,4-dihydro-6-methyl-5-pyrimidinecarboxylic Acid Esters as Potent Mimics of Dihydropyridines. J. Med. Chem. 1990, Vol 33, No.5, pages 1510-1515, especially Schemes I and II at page 1512.	10-12, 15-17
Y	US 5,155,174 A (CHANG ET AL) 13 October 1992 (13.10.92), see entire document.	10-12, 15-17
A	WO 94/08051 A1 (THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK) 14 April 1994 (14.04.94), see entire document.	1-57
A, P	BORMAN, S. Combinatorial chemists focus on small molecules, molecular recognition, and automation. Chem. & Eng. News. 12 February 1996, pages 29-54.	1-57

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/05956

Box I Observations where certain claims were found unsearchable (Continuation of item 1 f first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/05956

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

435/7.1; 436/518, 523, 527, 528; 523/213; 525/326.7, 375; 544/246; 546/1, 184

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-9, drawn to a library of compounds and claim(s) 10-19, 53, and 54, drawn to a method for preparing the individual heterocyclic groups covalently attached to a solid support.
Group II, claim(s) 20-37 and 55, drawn to method steps for preparing a synthetic compound library.
Group III, claim(s) 38-44 and 56, drawn to alternative method steps for preparing a synthetic compound library.
Group IV, claim(s) 45-51 and 57, drawn to further alternative method steps for preparing a synthetic compound library.
Group V, claim(s) 52, drawn to a library of diverse solid phase adducts.

The inventions listed as Groups I, II, III, IV, and V do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
The libraries of Groups I and V lack a special technical feature that defines a contribution over the prior art since many of these compounds are known in the art as evidenced by their existence in, for example, US class 523, subclass 213 and US class 525, subclasses 326.7, 327.1, and 375. Note the attached class definitions.
The inventions listed as Groups II, III, and IV are alternative methods for the production of the invention of Group I. These alternative methods lack unity of invention since the applicants are entitled to the examination of only one such process without the payment of additional fees. See MPEP, Annex B, Part 1, paragraph (e).